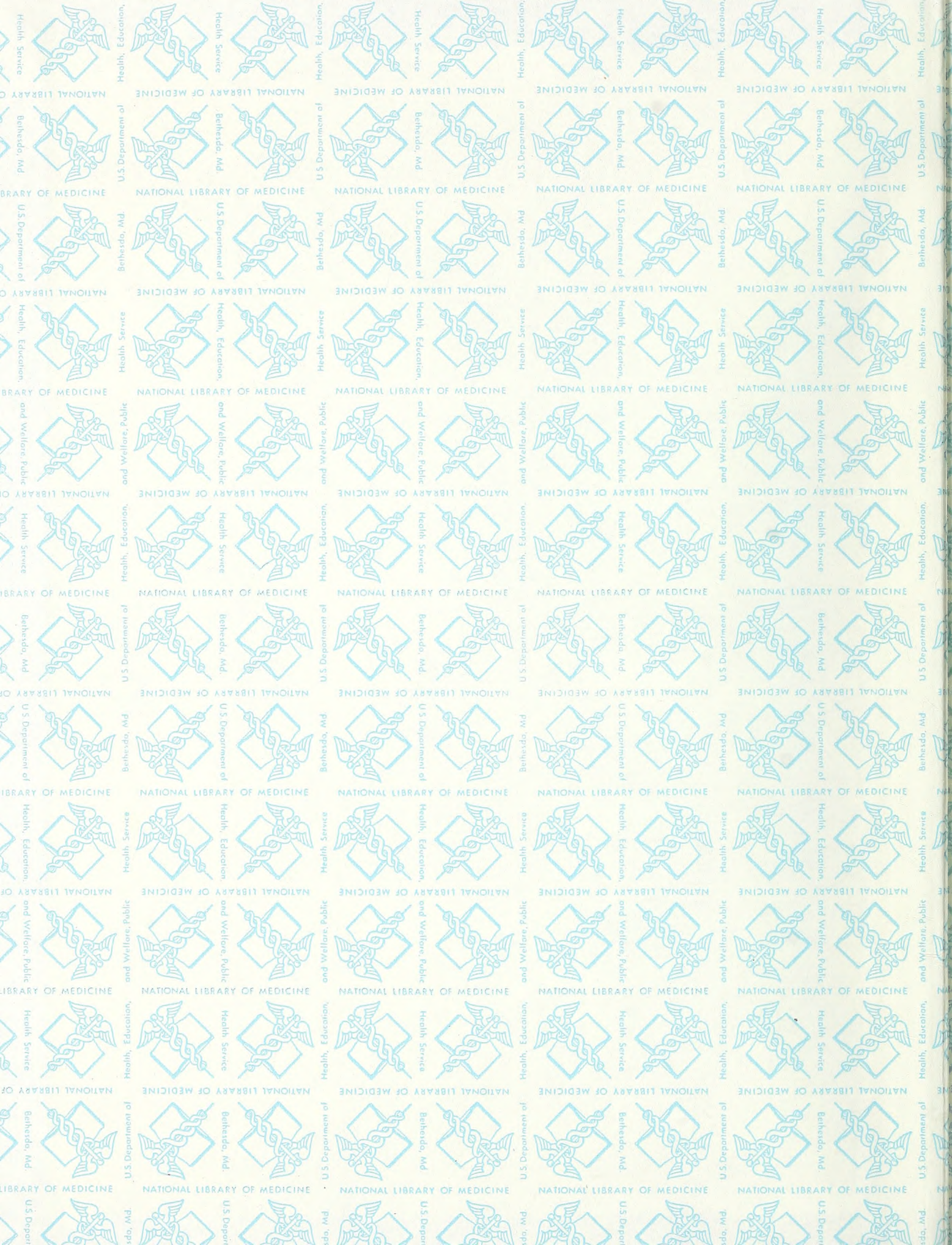


SPEECHES, ARTICLES, AND
SELECTED PAPERS

Donald S. Fredrickson, M. D.

1975-1981

Volume 3





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1979-81
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Speeches, Articles, and Selected Papers
Donald S. Fredrickson, M.D.
1979-1981*
Volume 3

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National Institute of Health (NIH)
Office of the Director

SPEECHES, ARTICLES, AND SELECTED PAPERS

Donald S. Fredrickson, M.D.

1975-1981

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

January 10, 1979

Senior NIH Scientists:

Hans Stetten wishes to step aside from the post of Deputy Director (Science). I accept his request with great reluctance and only with the provision that he be available to me a while longer in some other capacity.

I should like to postpone to a happier occasion a summing up of all the ways Dr. Stetten has served science and medicine with distinction. I do want to acknowledge here the virtuous combination of high science, humaneness, and honesty with which he has graced his present position at NIH.

The NIH Intramural Research Program, for which the Science Deputy is primarily responsible, is a reflection of certain qualities possessed by its present and past leaders. Among these are: a vigilant defense of free inquiry, passionate concern for how conclusions are drawn from experiments and for the words used to describe the results, an insistence upon excellence, and a warm tolerance for the differences between the many kinds of people required to sustain so complex and remarkable an institution.

In seeking to recapture these qualities in Dr. Stetten's successor, we will be striving to preserve an unprecedented capability for research in the life sciences that is represented by NIH laboratories and clinics. The human and physical capital of the intramural program is awesome, and the power for continued accomplishment seems unlimited. Yet the essence of its greatness is fragile and could be quickly destroyed by careless trusteeship. It would be irreplaceable.

These precious resources are dedicated to a quest for reality in a world often distracted by fantasy. To ensure that this essential mission is always performed well, and is continually directed at problems that have importance to this or future generations, is a responsibility that we accept in the name of the public.

As a senior scientist and scholar in intramural NIH, you share with me a deep interest in the organization and leadership of campus scientific activities. While I would like now to meet personally with all of the intramural community to discuss these common interests, this will not be practical. I will, however, be inviting some of you to meet with me over the next several weeks for that purpose.

I hope that, either directly or through your peers, you will all communicate your suggestions to me as the search for new leadership begins.

Sincerely,

Donald S. Fredrickson, M.D.
Director

Remarks before Dr. Martin L. King, Jr. Commemorative Birthday Celebration, January 17, 1979.

For several years now NIH has participated in this special day of recognition and remembrance for one of America's great heroes -- Dr. Martin Luther King, Jr. I am happy that we are continuing that fine tradition and I'm pleased to be a part of it personally. And I'm very proud of the fact that the NIH Cultural Committee for Black History Observance has arranged such a splendid program today.

It is certainly fitting that we pause to commemorate Dr. King's birthdate. The purpose of this observance is to honor him for his many contributions to the betterment of our society. *

In this, I believe we at NIH have a special place. Our goals, like those of Dr. King, are to release human potential and to promote human independence and dignity. Dr. King approached these goals through his ministry and his great powers of suasion. We approach ours through the process of research and discovery. But we are linked in our dedication to the cause of human betterment.

It is a special honor for me to introduce our guest speaker today.

John Conyers has represented the first district of Michigan in the United States Congress since 1964. In 1978 he was reelected to his eighth term in the U.S. House of Representatives with 93 percent of the vote.

Congressman Conyers was born and educated in Detroit and received his degree from Wayne State University. He has been active and in leadership positions in the trade union and civil liberties field for more than 20 years.

- 2 -

In fact, Mr. Conyers received the Rosa Parks Award for Civil Rights Activities in 1967 from Dr. Martin Luther King, Jr. himself. I can think of few more appropriate people therefore to bring us a message in the spirit of Dr. King than John Conyers.

It is a pleasure to present to you Congressman John Conyers of Detroit, Michigan.

D R A F T - 2/6/79
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NOTES ON AN EDITORIAL

In an editorial in Science (January 5, 1979) Singer has described her perceptions of the outcome of the two-year effort culminating last month in new NIH guidelines for recombinant DNA research. Under the title "Spectacular Science and Ponderous Process," she gives her account in the tones of a requiem for lost independence and time, and implies that NIH (acting for science) has yielded its sword to HEW bureaucracy. My memories of the ordeal cannot be very different from hers, but I have assessed the outcome differently. I think we have won a significant victory over a dangerously excessive reaction first set in motion by scientists. NIH will shortly issue the fourth volume of its public record on "the DNA controversy." From such raw material contemporary scientists or future historians must draw their own conclusions about the setting in which the 1976 guidelines were revised and whether the changes introduced in the final review process were necessary or even worthwhile.

Singer states that the HEW Secretary and his staff "have now assumed direct supervision of recombinant DNA policy-making." The new guidelines, however, continue the full delegation of responsibility for administration to the NIH Director and now give him the authorities for revision that the old guidelines so seriously lacked. The Director must exercise his discretion

under demanding procedures and standards. These have been created, however, to reassure the public and other Federal agencies that they, too, may participate, and are not designed to lever the Secretary and his staff into the chain of decision making. The detailed analysis led by the HEW General Counsel undoubtedly added a few weeks to the long period of revision. A modest additional burden of procedural safeguards was one result. Another was the stripping away of any grounds for further complaint from the most fervent dissident that the public had not been exhaustively consulted or that adequate provisions had now not been made for external surveillance of what scientists are doing with techniques for recombinant genes.

As part of the latter concession, the Recombinant DNA Advisory Committee (RAC) was changed. Generally, a two-level review has been accepted as the model for scientific advisory apparatus, the first, a technical review by the experts (the study section), followed by the policy review involving both scientists and laymen (the Advisory Council). The Director's Advisory Committee (DAC) previously was used to fill this bicameral requirement under the old NIH guidelines. The 1976 rules, however, were devoid of most discretionary authority. Our experience with the DAC also suggested that DNA technology was too complex a subject for non-experts to cope with under the traditional two-tiered system. It emerged that, when the non-expert is unable to comprehend so much of the details, his "public policy role"

must be performed in the midst of the experts. Here, at the least, the layman is in a position to see if the experts appear to be listening to each other and paying attention to the evidence. Moreover, for performance of the case-by-case analyses required of RAC, and upon which forward movement in many laboratories is dependent, two stages of advice preceding the Director's review and decision will create intolerable delays and confusion.

Singer is right, though, to sense that compression of RAC into a single, mixed advisory group is dangerous. It becomes especially so if well-meant attempts to "balance the views" result in polarization and paralysis. The new committee shares an enormous responsibility to suppress both partisan and theosophical tendencies. The new RAC is the most visible of current experiments in lay participation in scientific process. We all may have to travel across the "moral gap" on the bridge that its members will be attempting to construct.

In the anxiety created by the reconstitution of the RAC, some of the major achievements of revision have gone without notice. The new guidelines retain every important substantive change proposed by NIH and its scientific advisors. There is provision for continuous and orderly evolution of the rules--even to their eventual elimination when the need disappears. Many experiments now judged to be harmless are exempted, and a reduction in containment for many important kinds of experiments

experiments has been decided upon. The discretion and responsibility for following the rules also have begun to return to the research institutions, where they properly belong.

If we read the portents correctly, moves to enact statutory regulation of recombinant DNA experimentation now are not likely to be revived. Given the medieval features of the first-laws proposed and the difficulty of eliminating all such features in subsequent attempts, this is significant blessing for science as well as the rest of society. The diminished thirst for legislation is partly due to evidence that the dangers have been exaggerated. The actions of the Secretary in requesting FDA and EPA to use their existing authorities to extend the guidelines over research in the private sector have also been helpful.

Probably the exemplary cooperation and patience of the scientists whose work has been at stake during this long evaluation has contributed most to slow restoration of public confidence on the side of science. This being so, it is disappointing that an elitist image of science, including a sacred right of self-determination in technical matters, should be cast as the ultimate argument against the new use of the guidelines. It seems to me that the survival of the elite in our time must depend more on the ability to accept popular challenge to self-determination and to win the arguments in the open on the merits of the case.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

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Spectacular Science and Ponderous Process

Since 1973 substantial effort has been made to deal prudently with the concern that recombinant DNA experiments might prove hazardous. Unprecedented restriction of experiments was asked of a community bred for independence of mind and spirit. Despite widespread skepticism that hazards actually existed, the effort to minimize risk was a remarkable success, primarily because of the respect accorded to those scientists who called for prudence and later to the National Institutes of Health (NIH) as a scientific institution. To produce standards of laboratory safety, NIH formed the Recombinant DNA Advisory Committee (RAC) made up of prominent scientists, who developed the Guidelines for recombinant DNA research published by NIH in June 1976. Under the Guidelines work has proceeded safely and research accomplishments have been spectacular.

The confidence of the scientific community in the wisdom behind these efforts is rapidly eroding. Responsibility for the erosion lies with the Secretary of Health, Education, and Welfare (HEW) and his staff, who have now assumed direct supervision of recombinant DNA policy-making, and who have adopted procedures unsuitable to the complex problem of controlling creative activities. Two developments that have already had unnecessary adverse consequences are particularly disturbing.

First, there has been a long delay in promulgating amply justified revisions of the Guidelines. These were produced in July 1978 by NIH and its advisory committees, who gave unprecedented attention to comment by the scientific and general public and produced a document with broad support. Yet HEW imposed still another round of review; assurances that it would be expeditious proved empty. Experiments critical for realizing the practical and intellectual promise of recombinant DNA and for making risk assessments have been held up for months.

Second, the authority to appoint RAC members has been transferred from NIH to HEW. Contradicting its own definition of good process, HEW considered new members without adequately consulting the scientific public and in disregard of much of NIH's advice. In response to NIH urging and intervention by an alerted community, the most misguided inclinations were finally corrected. These had included questioning the qualifications of an eminent molecular biologist, himself one of the first to call for caution; questioning the independence of NIH scientists serving as RAC members; and consideration of individuals known to be intractably opposed to the research. Nevertheless, the insensitivity of HEW to vital issues is still apparent in the makeup of the new RAC. The RAC's job will be to advise the director of NIH on highly technical matters. The revised Guidelines require that 20 percent of its members be nonscientists and that major actions be published for comment before adoption. This should have been sufficient to protect the public interest and still allow for the expertise required to deal with scientific matters. But under recent proposals the new RAC (about 25 members) will have seven to nine (depending on how one counts) nonscientists and only token representation in the molecular biology of eukaryotes. In the absence of adequate expertise in relevant areas and with a lack of sufficient distinguished scientific leadership, it will be difficult for the reconstituted RAC to win respect for the Guidelines.

Lincoln Kirstein wrote, "Despite the populist politicians, certain crafts must live by elitist criteria." He included science as one of those crafts. When an egalitarian and humane society decides to support such a craft, public officials have the delicate task of nurturing elitist criteria while protecting the general interest. In the present case the two are interdependent, since safety depends on the diligence and therefore the confidence of individual investigators. Neither scientific criteria nor the public interest has been well served by HEW's actions.—MAXINE F. SINGER

*New York Review of Books, 23 November 1978.

STOCKHOLM REFLECTIONS*

DONALD S. FREDRICKSON†

We all went to Stockholm for the meeting.¹ The impressive auspices—the Royal Swedish Academy of Sciences and a Nobel Symposium—along with seductive images of Scandinavia in summer—birches along the Baltic and reflections of the night sun from golden towers—conspired to draw us there.

Mild shock marked our arrival as dreams of comforts and the Grand Hotel were snuffed abruptly. Amenities of a simpler sort, we learned, were offered at Södergarn, a seminary-dormitory-reformatory at safe remove from urban distractions and designed for intensive contemplation. The object of this was not left to our imagination. Spelled out across the classroom slate was our assignment: ETHICS FOR DECISION-MAKING IN SCIENCE.

Here the moral essence of science was to be distilled again, and our hosts had carefully mixed the starting brew.² My fellow contemplatives were scientists, but so great was the diversity among us that we did not even seem to have a common profession. By and large we were mainly strangers, although here and there was a friend or acquaintance.

The Philosophers came first, their priority resting on a parent's illusion that he best understands his own child. They had the grace to spare us the more depressing parts of the philosophy of history and the history of philosophy. They left out the cycle of Polybius—his gloomy view that no human institution is capable of lasting improvement. There was no mention of "moral terrorism," Kant's term for the awful Protestant doctrine that we not only fail to improve but steadily regress.³

*Address delivered at the University of North Carolina Convocation in recognition of the Medical School's Centennial, Chapel Hill, North Carolina, February 10, 1979.

†Director, National Institutes of Health, Bethesda, Maryland 20014.

¹In constructing a short allegory for purposes of the convocation honoring the centenary of the School of Medicine at the University of North Carolina, I have taken liberties with even my own perceptions of a Nobel Symposium held August 21–25, 1978. The proceedings are to be published.

²Our hosts may have had private motives in seeking participants who did not resemble the cast of a previous Nobel Symposium. After participating in that one, Arthur Koestler wrote an unflattering description of international scientific conferences [1].

³For further insight into the debate on moral destiny, I recommend Frank E. Manuel's *Shapes of Philosophical History* [2].

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As scientists tend to be, we were more at home among the eighteenth-century French with optimists like Condorcet and Saint-Simon and their fellow "philosophers of perfectability." In order to ride the crest of its potential, implied the Philosophers, science must be propelled by faith that man's salvation and survival are tied more tightly to reason than to any other human quality.

But we were next to hear from some of our coreligionists, who believed that science itself is badly in need of salvation and, as they saw it, partly from sins of its own.

Affirmative Action struck early. In bitter tones she complained wearily that in her native France half of the people, but only a quarter of the scientists, are women. I wondered what she would say if she knew that among the professionals in American laboratories her sex numbered less than one in five. I rose to express sympathy with her cause if not with her proposed solutions.

"I believe there are slights and harassments," I said, "of which we males often lack awareness. There is also dismal scarcity of some ethnics among the ranks of scientists. Worst of all is the length of time it will take before these faults can be corrected."

With a gesture saying she had heard all this before, Affirmative Action exclaimed impatiently, "You are patronizing me!"

At that, Third World spoke up. "I think he's innocent of condescension. As a woman *and* a black, I have some feeling for this sort of thing."

This act of rescue done, Third World went on speaking. Perhaps the thought of being patronized, now aroused, would not lie down again. "In a developing country," she mused, "we sometimes wonder if we will ever get 'developed.' Or if we will know it when we finally are."

Her gentle ironies caused regions of the globe to light up over the surface of our minds. Visible were the boundaries between affluence and poverty, between resplendent institutes and makeshift laboratories. Were there also contour lines for ethics or morality? Surely not, we concluded; the strength of science is that it can determine truth according to universal rules.

The Marxist took the floor. The true morality, he declared, lies in whether the scientists are working for the people. And he suggested that this could not be guaranteed unless priority for experiments was a truly popular (or Party?) choice.

This touched raw nerves around the room. Recent wounds of recombinant DNA debates began to hurt again. Some later said they heard in a dusty corner of their minds echoes of that stale refrain, "Science is too important to be left to the scientists."

These distractions, however, should not deafen us to the seriousness of talk that followed. The question of how citizens, professional and lay, might chart together the course of scientific experimentation is a

dilemma of recent vintage. It is prompted most by fears for public safety and demands for equity in the use of public funds.

Within science the choice of subject traditionally rises from multiple foundations. The first, or deepest, is an objective judgment of the quality of hypothesis, or scientific question, and the way to test it. Most scientists see these technical choices as their crucial and inviolable prerogative. Then, on this base can be laid subjective or value judgments that will determine a social priority for the undertaking. In these joint considerations, there is always some gap between the perceptions of the issues by the expert and the layman. This "moral" gap is usually filled with a mix of mutual trust and procedural protection. There are those who judge that too much trust can be dangerous; it is clear that an excess of procedure can be fatal.

Are there alternative formulas for bridging the gap? At Södergarn, a Scientist Laureate wished to address that subject. He was a nuclear physicist, elevated to the Nobility by his scholarly peers and countrymen. Long opposed to expansion of breeder reactors, he now sought contrition for the inventions that had made them possible. He had a solution to the control of "dangerous" discoveries: deny the Prize to anyone whose findings—however fundamental—have some potential for harmful use. Make the explorer tell precisely where he intends to land or give him no ship and no license to sail . . . and deal harshly with any who stray from the course!

If the Doctrine of Forbidden Knowledge had other friends, they stayed silent.

Someone—perhaps it was the Sponsoring Foundation—commented softly, "After all, the Prize itself was a penance."

Another mumbled a query for the Laureate. "Would you cut off a baby's hands because it might someday become a thief?"

There were strong protests that suppression of discovery would mean the death of science. Science, said the voices, will serve mankind in proportion to mastery of the technology extending from discoveries. I think we could have convinced the Laureate of the logic in this distinction. Yes, surely we would have done so . . . had it not been for Disarmament.

Despairing, bone-tired, Disarmament talked at length on the danger of technology growing out of control. All the Sciences (Big and Little, For-Profit and Not-for-Profit, Government, Academic, East, West, Hard, Soft) listened carefully, each engrossed in private thoughts. First came the chilling litany of progressive "technical improvement." But who could deny that science had led the way from Alamogordo to the neutron bomb? We could not, admonished Disarmament, erase our footprints, leaving only the traces of the engineers, generals, and others who had trod the deadly path.

Disarmament then led us through hyperbole of an even grimmer kind. "We could look back to 1961," he said. "Then the world's supply was but 3,000 'primitive' bombs—barely enough to destroy all civilization. But the insane race continues. Now the nuclear arsenals are believed to hold the equivalent of 4 tons of TNT for every man, woman, and child.⁴ In a time of multiplying scarcities, we seem to have a growing surplus on the earth—one measured in terms of overkill per capita."

"But this," someone bleated, "is the work of politicians, not of scientists."

And we believed him passionately, for we said we had not participated in the escalation. It is citizens, we insisted, who must exercise their options here. Yet, at a deeper level, we knew that we too are citizens and with special gifts of knowledge. We wondered: By choosing to be silent on some matters, do we forfeit our right to criticize the ethics of others?

Toward the close of the final day, the inevitable resolution was presented by some veterans of this practice. It began, "The Nobel Symposium on Ethics and Science Policy has considered the pernicious social consequences of science and technology. . . ." And it ended, "We urge scientists to take their social responsibility far more seriously."

The resolution did not pass—not because of its casuistic faults, but because of its assault on private concerns, ambiguities that ran more deeply now than before we came.

"The road to hell is paved with resolutions," said a faint, familiar voice.

We turned to look. Yes, it was University, veteran of confrontations and resolutions.

"You have been strangely silent up to now," we scolded. "Do the more meaningful curriculums no longer 'relate' to issues of ethics or morality?"

"Others have become accustomed to speak about such matters in my place," grumbled University. "I am mortgaged to government grants and capitulations and bound by the terms thereof. The scholars have grown expert in adversarial techniques and are divided along lines of special interest. In this poor season, there is some loss of solidarity, and perhaps of nerve, in my communities."

No lesson replayed at Stockholm was more important than the last. Among all social organizations, the University is best prepared to nurture both the body and the process of science. None of us, including the leaders and faculties of the Universities, may dare to forget the responsibilities this implies.

What are the principal tasks? Every educated layman must be brought to understand something of the scientific process, its requirements and

⁴The statistics on nuclear weapons in 1961 and their current TNT-equivalent per capita were estimated by Frank Barnaby in his symposium paper "Ethical Dilemmas in Weapon Development," to be published in the proceedings.

limitations. Many more people must gain the competence to hold their own responsibly in decisions on technological commitment. Fair opportunity must be given to people of different kinds to make science their profession. The scientists must be enabled to perform at full potential and to understand the social obligation such opportunity imposes.

To prepare these kinds of citizens, which the times demand, we depend upon education. Laws, governments, churches, factions, even resolutions can help; but none compares with the latent power of the University to cultivate passion for truth, love of reason, and high tolerance for dissent. These are the qualities essential for science, and for the making of decisions about science in a democratic society.

* * *

I have just suggested that the universities need to be heard in greater strength and perhaps more harmony in current debates on science. It would be a fair criticism of my Stockholm images if you retorted that the university has always meant to be a beacon for the individual rather than a spokesman for the crowd.

One hundred and ninety years ago, the people of this state, mindful of the future, caused a lamp to be lit in Chapel Hill. It was to guide the people of the farms and towns of North Carolina to a better life and a sense of lasting values. The light has grown stronger through the years, reaching beyond the state, over the nation and the world—helping to illuminate the paths of mankind everywhere. Today's convocation commemorates an event of consequence in the history of this institution—the founding of its School of Medicine a century ago. I think it significant that this now illustrious school began and continues as an organic part of the university. It is a wise recognition of the truth that science best serves as a base for healing when fostered in the company of all the arts and humanities. It is also in such a place that science can serve man in ways that seem closest to God's intent.

REFERENCES

1. A. KOESTLER. *The call girls*. New York: Dell, 1973.
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INTRODUCTORY REMARKS 1/

by

Donald S. Fredrickson, M.D. 2/

Few conferences held here have centered upon subjects of direct concern to so many as this. Pain is a problem which affects one out of four of our total population each year. It is a cause of disability and a source of dread for millions.

At a time when spectacular advances have been made in understanding and treating many disorders, it is sobering to recognize how limited is our knowledge of pain and its mechanisms. Not only is there a deficiency in knowledge, but a general failure to apply adequately and properly even that which is known, especially for the treatment of chronic pain or that associated with terminal illness.

In recent years a growing number of scientists, physicians, and lay persons have insisted that we can--indeed must--improve our treatment of pain and discomfort as well as provide truly humanitarian care of the terminally ill.

Today's portion of the conference will be devoted to understanding of pain--tomorrow morning's to its treatment.

Because of my personal commitment to Consensus Development as a means for sorting out and facing important issues related to medical care, I am especially interested in the final segment of your Conference Friday afternoon.

1/ For presentation at the Conference on Pain, Discomfort, and Humanitarian Care, Masur Auditorium, Clinical Center, NIH, February 15, 1979

2/ Director, National Institutes of Health, Bethesda, Maryland

March 1, 1979

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Statement by the Director

I am here to discuss with you today the 1980 budget request for the National Institutes of Health.

Although the figures in this budget are approximately identical to the 1979 appropriation, I come before the Subcommittee to assure you that the various programs of the NIH will be able to continue the level of excellence you have come to expect of us.

Maintenance of this level in a time of severe budgetary constraints represents a firm commitment by the Administration to the notion that the individual and societal costs of disease and disability can best be reduced through development of new approaches to prevention and treatment—approaches that depend in large measure on elucidation of the mechanisms underlying fundamental biological processes and an understanding of what happens when these fail or are altered to produce disease.

Maintenance of a level budget will impose difficult choices in the management of the biomedical research enterprise, and I am pleased to report that we are making significant progress in our ability to deal with some of the choices we face.

We now classify all of our programs as they relate to the four areas comprising the NIH mission to improve the Nation's health. The first of these, termed the science base, accounts for 74 percent of

the overall 1980 NIH budget request. It is science after all—the acquisition of new knowledge—which provides us with the tools we require to develop the ultimate means to reduce health care costs through preventing and treating more efficiently disease and disability. Thus, the manner in which research results are put to use comprises our second category—application—which depends intimately and entirely upon the success of our research programs. The third category, which we term "transfer", is an essential function of NIH and simply means that, once we know something important, we must make sure that the rest of the world knows about it too, and as soon as possible. It is especially important that physicians and health professionals put into use the most advanced methods available without delay. The fourth category, training, is, of course, the means by which the NIH and the Nation can continue the high quality of research for which we are acclaimed.

I cannot over-emphasize how absolutely vital the continued support of NIH's science base must be. I would like to take just a few moments to illustrate some of the recent advances in biomedical research and how this new knowledge is continually offering us potentially beneficial applications. The history of science is replete with examples to support this view. Recent advances in the use of recombinant DNA techniques have yielded new insights into the structure and regulation of genes, offering the possibility of commercial production of scarce biological products, such as insulin and growth hormone. It has moved us several steps closer to knowing the underlying causes of cancer, and to realizing the effective treatment of some genetic diseases. "Basic"

research in receptor sites--characterizing the interaction of hormones and cell surfaces--holds promise for the treatment of endocrine diseases such as diabetes. And investigation of the differences between normal and cancerous cells, while directed at the most fundamental biological processes, has significant implications for the diagnosis and prevention of cancer.

Certain elements of the science base deserve special mention. As Congress has recognized in recent hearings and reports, the primary mechanism for knowledge development is the investigator-initiated research project. Approximately 43 percent of the 1980 funds requested will support extramural research projects, allowing us to fund about 20 percent of approved competing grant applications. Supplementing the individual and program research projects are the research centers, where multidisciplinary interaction and support enable us to focus research in specific areas, such as heart disease and cancer. I share this Committee's concern that NIH grant programs be supported by a strong peer review system, and I am pleased to report the addition of four badly needed new study sections whose charters have recently been signed by Secretary Califano.

Our own intramural research program, conducted mainly in laboratories and clinics on and near the NIH campus, engages the efforts of approximately 60 percent of our staff. Evaluations of this program have repeatedly shown that intramural scientists' contribution to the science base far exceeds that which one would expect, based on their numbers. A recent evaluation shows the output of "most cited papers" between

1961-1975 by NIH intramural scientists to have exceeded by far any university in the world. There is no question that this select group of highly competent individuals, which includes four Nobel laureates, represent a major national asset, providing leadership to the biomedical research community and serving as a valuable resource to the extramural program staff.

The Clinical Center on the NIH campus provides unique opportunities for bringing the intramural science base to the point of application, a capacity that will be greatly enhanced by completion of the Ambulatory Care Research Facility. The final funding for the ACRF was provided last year, and construction is progressing smoothly; we look forward to its opening in 1982.

The application of research findings and development of interventions aimed at specific problems of health and disease represents the next step in the research continuum. Among the more exciting topics to be explored are development of systemic anti-viral agents and application of positron emission transverse tomography (PETT) for diagnosis of intracranial lesions. Also planned are several major clinical trials, including a joint effort between NHLBI and NIA to determine the effectiveness of lowering blood pressure in the elderly.

In recent years we have made significant progress in fostering the transfer of research findings to the health care delivery system. The Office of Medical Applications of Research, now officially established, serves as the focal point for NIH transfer activities, as well as a link to the broader mandate of the new National Center for Health Care

Technology. One of the key elements in this process is the development of consensus about treatment modalities. Over a dozen conferences have been held on a number of topics for this purpose and several more are planned. In keeping with our heightened interest in prevention, we have recently concluded a conference on antenatal diagnosis. The proceedings of these meetings are disseminated to both scientists and practicing physicians to further inform the general public.

The training of biomedical investigators remains one of the most critical activities supported by the NIH. All of our research training programs have now been consolidated under the National Research Service Awards program, and recent amendments to that law have done a great deal to make these awards more attractive to young scientists. The NIH has put forth a great deal of effort in the past year to develop a training policy truly responsive to the Nation's needs for the training of research personnel, as recommended by the National Academy of Sciences. The 1980 budget contains a modest increase for research training, which will be directed primarily toward training of epidemiologists and environmental toxicologists, who are needed to implement the new incentives in disease prevention. The budget request will provide for the training of approximately 10,900 investigators, an increase of some 375 over the current year's program.

Within the budget request, several areas of emphasis have been identified. Foremost among these is the Secretary's initiative in

prevention. Much of the NIH program is, at least indirectly, related to prevention, because the ultimate objective of most biomedical research—the understanding of life's most fundamental processes—will provide us with the means to prevent disease and disability. The redirection of funds within the budget will permit more rapid exploitation of certain high-priority areas, particularly those which lend themselves to enhanced cooperation and coordination among the Institutes of NIH and between NIH and other agencies. For example, toxicology research will be expanded to include additional studies of the effects of environmental agents and pollutants on human health, and the training of additional environmental toxicologists. This expansion will take place within the newly established National Toxicology Program which will provide coordination, under the leadership of the Director of the National Institute of Environmental Health Sciences, of all the Department's programs in toxicology.

International health is another area to be highlighted, focusing primarily on tropical disease and infectious diseases of international concern. The National Institute of Allergy and Infectious Diseases will serve as a focal point for international collaboration between the United States and foreign investigators.

As mandated by the Congress last year, diabetes continues to be an area of strong emphasis in many of the NIH Institutes. Recently, I directed the National Institute of Arthritis, Metabolism, and Digestive Diseases to assume the leadership role in coordination of all NIH diabetes research activities. It is our hope that this will serve as a model for

management of the many crucial research efforts that cut across Institute lines. The NIH commitment to diabetes research will continue to be strengthened in 1980, and the budget request includes an estimated \$125 million for diabetes research.

Nutrition is another area of trans-NIH interest which offers great promise for the management and possible prevention of many disease states. Its importance is highlighted by the many Congressional mandates directed at NIH and other agencies. Research in nutrition continues to shed light on ways in which the body utilizes nutrients and how certain dietary substances may be related to diseases with a high incidence in the American population. We are expanding our support of clinical nutrition research units to include core grants for shared facilities combining research, training, and service. We expect to have several such units underway by the end of the year.

Mr. Chairman, I and the other Directors will be pleased to try to answer any questions that you or your colleagues may have.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Statement by the Director

I am here to discuss with you today the 1980 budget request for the National Institutes of Health. Our budget for fiscal year 1980 is the same as our 1979 appropriation level. I assure you that we can preserve a strong capacity for biomedical research in this country in the face of austerity. Maintenance of a level budget, however, will impose difficult choices in the management of the biomedical research enterprise.

For the past several years we have been developing new methods for describing the allocation of NIH resources. We have also conducted intensive annual reviews, Institute by Institute, of our priorities for research across the continuum of inquiry in biology and medicine. These priorities must represent a balance between the needs for biomedical knowledge, the technical opportunities to acquire it, and the resources available to support investigation. Mention of certain support mechanisms and research programs will recur during the hearings on this budget, Mr. Chairman, and it may be useful for me to take a moment to set them in perspective.

We group our activities at NIH into four main categories, a combination designated by their initials as the SATT system. The first category, the Science Base, accounts for between 70 and 75 percent of the overall 1980 budget. Science base means "basic science" and the resources necessary to facilitate it. Basic science refers to laboratory and clinical research that is seeking

new knowledge without a specific or immediate aim toward application-- knowledge that, when synthesized with other information, will someday lead us to interventions that will have a positive effect on health. Most science base support goes to one of three main groups: research project grants, institutional grants that underpin these activities, and intramural research.

Investigator-initiated extramural research is carried out under research project grants, mainly ROIs and POIs, a subject of considerable discussion last year, as the committee will recall. Approximately 43 percent of the 1980 funds requested will support extramural research project grants. This is the same percentage as in the 1979 appropriation. This year we will be able to fund an average of about 20 percent of approved competing research project grant applications. Last year's figure was 43 percent; the difference is due to an increased base of non-competing grants, inflationary increases in this continuation base, and a larger number of applications. The approved applications are funded on the basis of scientific merit, as reflected in priority scores assigned them by Study Sections and on judgment of program relevance by Advisory Councils. I share this Committee's concern that NIH grant programs be supported by a strong peer review system, and I am pleased to report the addition of four badly needed new study sections whose charters have recently been signed by Secretary Califano. All of our grants, which include others awarded to multidisciplinary centers, and our contracts, are awarded on the basis of peer review.

Our own intramural research program, conducted mainly in laboratories and clinics on and near the NIH campus, engaging the efforts of approximately 60 percent of our staff, is also found within the science base. Evaluations of this program have repeatedly shown that intramural scientists' contribution to the science base far exceeds that which one would expect, based on their numbers. There is no question that this select group of highly competent individuals, which includes four Nobel laureates, represent a major national asset, providing leadership to the biomedical research community and serving as a valuable resource to the extramural program staff.

The institutional support included in science base funding includes Biomedical Research Support Grants, and maintenance of shared instrumentation, clinical research centers, and primate centers.

I cannot overemphasize the importance of continued strong support of the NIH's science base. Knowledge, as we all know, gives us power. What we learn in research today will provide the basis for our health practices tomorrow. We are, I believe, on the brink of a number of major biomedical breakthroughs. Although I cannot say when, I feel strongly that current studies on genetics and cell transformation will lead us to some causes of cancer. We will soon be privy to the secrets of auto-immune diseases and will be able to have new, powerful impacts on the quality of life at every age, not only in our country but around the world. I would like to take just a few moments to illustrate how new knowledge is continually offering us potentially beneficial applications. Recent advances in the use of recombinant

DNA techniques have yielded new insights into the structure and regulation of genes, offering the possibility of commercial production of scarce biological products, such as insulin and growth hormone. It has moved us several steps closer to knowing the underlying causes of cancer, and to realizing the effective treatment of some genetic diseases. "Basic" research in receptor sites--characterizing the interaction of hormones and cell surfaces--holds promise for the treatment of endocrine diseases such as diabetes. Vaccines for diarrheas that kill tens of thousands of children in the world, and perhaps for other parasitic diseases are looming as possible; cancer cure rates are rising and spectacular decreases are continuing in mortality from cardiovascular disease.

Perhaps the hardest choices come in the next category of biomedical research, that of applications of research. This is scientific development seeking to achieve practical use of knowledge through research. It is at this point that we further develop and test the means for preventing a disease, improving diagnosis, producing relief or offering a cure. Most of our clinical trials are included in this category. They are concerned with the perfecting of vaccines; the testing of drugs, techniques, products, instrumentation; the improvement of medications; the improvement of diet.

The Clinical Center on the NIH campus provides unique opportunities for bringing the intramural science base to the point of application, a capacity that will be greatly enhanced by completion of the Ambulatory Care Research Facility. The final funding for the ACRF was provided last year, and construction is progressing smoothly; we look forward to its opening in 1982.

The third category we term Transfer. It is at this point that we make certain that those delivering health care and the general public learn as soon as it is possible about answers available to the questions they have about health and disease. We accomplish this transfer through field trials, demonstration projects, and consensus development. The Office of Medical Applications of Research, now officially established, serves as the focal point for NIH transfer activities, as well as a link to the broader mandate of the new National Center for Health Care Technology. One of the key elements in this process is the seeking of consensus about new interventions for prevention, diagnosis, or treatment. Over a dozen conferences for this purpose were held at NIH last year on a number of topics and more are planned. The proceedings of these meetings are disseminated to scientists, practicing physicians, and laymen, and the responses have been more than positive.

It is in the area of transfer that we must recognize the unique resource America has in the National Library of Medicine. In making choices as to how we use our funds, it is essential that we keep in mind the importance of continued support for this major conduit for biomedical information.

There must be a continuing renewal of creativity and energy in a process like scientific research. New people must be trained in a steady supply. Therefore, the training of biomedical investigators remains one of the most critical activities supported by the NIH. About 25 percent of the new entrants into biomedical research are

supported by Federal training programs. We have evidence that this is a fraction upon which continued quality research is crucially dependent. All of our research training programs have now been consolidated under the National Research Service Awards program. Recent amendments to that law have done much to make the provisions of these awards more attractive to young scientists. The NIH has put forth much effort in the past year to develop an integrated training policy truly responsive to the Nation's needs for the training of research personnel, and is working closely and effectively with the National Academy of Sciences to maintain the most rational basis for training allocations. The 1980 budget contains a modest increase for research training. It will be directed primarily toward training of epidemiologists and environmental toxicologists. The 1980 budget provides for the training of approximately the same number of investigators as the previous year. However, offering a reasonable stipend to those being trained is enormously important. We are considering carefully the need to increase the stipends, even though doing so will reduce the number of applicants we can support.

One of the areas of emphasis in the budget request is the Secretary's initiative in prevention. This is being accomplished through the redirection of funds. For example, toxicology research will be expanded to include additional studies of the effects of environmental agents or pollutants in human health, and the training of additional toxicologists.

We will also be moving more rapidly in certain high priority areas, particularly those which enhance cooperation and coordination

among the Institutes of NIH and between the NIH and other agencies. For instance, the expansion of our efforts in toxicology research, which I have just mentioned, will take place within the newly established National Toxicology Program. As new as it is, this novel program has shown that coordination between the research and regulating agencies to meet a critical need can be accomplished effectively.

International health is another area to be highlighted, focusing primarily on tropical disease and infectious diseases of international concern. The National Institute of Allergy and Infectious Diseases will serve as a focal point for international collaboration between the United States and foreign investigators.

As mandated by the Congress last year, diabetes continues to be an area of strong emphasis in many of the NIH Institutes. Recently, I directed the National Institute of Arthritis, Metabolism, and Digestive Diseases to assume the leadership role in coordination of all NIH diabetes research activities. It is our hope that this will serve as a model for management of the many crucial research efforts that cut across Institute lines. The NIH commitment to diabetes research will continue to be strong in 1980. The budget request includes an estimated \$125 million for diabetes research.

Nutrition is another area of trans-NIH interest which offers great promise for the management and possible prevention of many disease states. Its importance is highlighted by the Congressional mandates directed at NIH and other agencies. Research in nutrition continues to shed light on ways in which the body utilizes nutrients and how certain dietary substances may be related to disease with a high incidence in the American population. We are expanding our

support of clinical nutrition research units to include core grants for shared facilities combining research, training, and service. We expect to have several such units underway by the end of the year.

In conclusion, Mr. Chairman, the NIH request for FY 1980 is \$3,172,430,000. I will be happy, as will the Directors of the Institutes and Divisions, to answer any questions you may have regarding our programs.

INTRODUCTORY REMARKS^{1/}

by

Donald S. Fredrickson, M.D.^{2/}

Good evening, ladies and gentlemen.

I am pleased to welcome you to this 28th annual Dyer Lecture. This distinguished lecture was established in 1950 to honor Dr. Rolla Eugene Dyer on his retirement as Director of the National Institutes of Health.

We are indeed fortunate tonight to have as our lecturer a pioneer in the elucidation of the precise molecular structure of antigens and antibodies. Dr. Elvin Kabat is Professor of Microbiology, and of Human Genetics and Development at Columbia University. He will speak to us tonight on the subject of "Structural and Genetic Approaches to the Study of Antibody Complementarity."

Elvin Kabat began as the first of a whole generation of immunologists who worked with or were inspired by Michael Heidelberger, who over a career that spanned six decades, guided the creation of the science of quantitative immunochemistry. Dr. Kabat was Dr. Heidelberger's first graduate student at Columbia University and served as his laboratory assistant between the years 1933 and 1937.

After receiving his Ph.D. in 1937, Dr. Kabat spent a year as a Rockefeller Foundation Fellow at the Institute of Physical Chemistry in Uppsala, Sweden, with The Svedberg, Arne Tiselius, and Kai Pederson, where he established that antibodies were "gamma globulins" whose molecular weights he determined.

^{1/} For presentation at the Dyer Lecture, 8:15 p.m., March 14, 1979, Masur Auditorium, National Institutes of Health, Bethesda, Maryland

^{2/} Director, National Institutes of Health

Dr. Kabat served as instructor in pathology at Cornell University Medical College between 1938 and 1941, when he returned to Columbia, where he became Professor in 1952. His research over the years has covered a broad range of problems, but a consistent theme of his work has been the elucidation of the precise molecular structures of antigens and antibodies, applying the basic techniques of quantitative immunochemistry in conjunction with structural carbohydrate and protein chemistry and physical chemistry. His principal research interests are the nature of antigenic determinants and antibody combining sites, the three dimensional folding of proteins and the structure of Blood Group substances. Dr. Kabat and Dr. Wu were the first who recognized the critical importance of limited regions of hypervariability, which he accurately predicted would be shown to be the complementarity determining regions of the combining sites of antibodies. X-ray crystallographic studies have subsequently confirmed this important prediction.

Dr. Kabat is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the World Health Organization Advisory Committee on Immunology. He has served as President of the American Association of Immunologists. His many honors include the Karl Landsteiner and Claude Bernard Medals, the Medal of the National Multiple Sclerosis Society and the Award of the 5th International Convocation on Immunology. In 1977, he shared the Louisa Gross Horwitz Prize with Drs. Michael Heidelberger and Henry Kunkel. He has been a Fogarty Scholar and is a consultant to the National Cancer Institute. In addition to maintaining his laboratories at Columbia, his present activities also include analyzing sequence data on immunoglobulins and antibodies in our PROPHET computer system here at NIH and making this valuable information available to the scientific community.

It is my great pleasure to introduce this year's R.E. Dyer
Lecturer,

Dr. Elvin Kabat.

A HISTORY OF THE RECOMBINANT DNA GUIDELINES IN THE UNITED STATES

D. S. Fredrickson

National Institutes of Health, U.S. Department of Health,
Education and Welfare, Bethesda, Maryland 20205, U.S.A.

On December 16, 1978, a telegram purporting to be from the Vatican was hand-delivered to the office of Joseph A. Califano, Jr., Secretary of Health, Education, and Welfare. "Habemus regimen recombinatum," it proclaimed, in celebration of the end of a long struggle to revise the NIH Guidelines for Research Involving Recombinant DNA Molecules. It was not the first telegram the Secretary had received on this subject. From Peking the preceding June, I had responded to his cabled instructions concerning proposed revisions of the Guidelines which I had taken to China. The U.S. liaison officers found my reply inappropriate for transmission, but I delivered it on my return, imprinted on a rice paper temple-rubbing.

These sophomoric tricks were moments of comic relief in a three-year period of coping with the scientific, political, and legal problems created by the advent of the "new biology". The following pages summarize my impressions of this turbulent experience.

My personal history of the DNA Guidelines in the United States recognizes three phases to date. Phase I is the period between the early concern about possible hazards of recombinant DNA technology and the delivery to NIH of proposed rules for conducting research. Phase II covers the promulgation of the NIH Guidelines in 1976 and the thirty months before their official revision. Phase III began on January 2, 1979, with a new set of rules painfully formulated during this unprecedented curtailment of experimentation in biology.

THE END OF THE BEGINNING

In this collection are reminiscences of the first apprehensions (1973), the decision to develop guidelines (1974), the Asilomar agreements (1975), and the exhausting constructions of the NIH Recombinant DNA Advisory Committee (RAC). Three versions of guidelines had emerged from RAC meetings after Asilomar. In La Jolla, California, on December 5, 1975, the Committee, with the "variorum" edition before it, finally succeeded in scaling conjectural hazards by parliamentary procedure. Chairman Hans Stetten went to the telephone to inform the NIH Director in Bethesda that the nation had acquired rules for recombinant DNA research. Much later I was told how he had returned to the conferees, shoulders drooping, success drained from his face. "He wants to have a public hearing on them", he mumbled.

PUBLIC AIRING BEGINS

From the beginning the decision to "go public" was variously understood and was resented by many. After all, the Director, NIH, has long had authority to promulgate guidelines for investigators the agency supports. There is no requirement for hearings or public comment. I became aware of new responsibilities heading my way sometime in the autumn of 1975, when I had been Director for only two or three months. At that time, I had barely heard of restriction enzymes and could not even have explained the crucial distinctions between Federal guidelines and regulations. From the first I was inclined—and after a little study and consultation, quite determined—to air in an open and public manner the scientific and social issues. This was the only way to decompress rising tensions and to prepare to defend whatever actions would be taken against certain criticism.

The Director's Advisory Committee (DAC) was convened in February 1976 for public discussion of the Guidelines. The transcript, like all the other relevant documents on the subject, is available in the "public record" published by NIH.¹ The hearing demonstrated the difficulties of holding a town meeting on molecular biology and exposed the full range of opinions on the risks of the new technology. It was apparent that our decisions would have to run a gamut of adversarial reactions and that some, in the end, might well be tested in the courts. After the hearing, the voice of Judge Bazelon lingered longest in my mind: "... the healthiest thing that can happen is to let it all hang out, warts and all, because if the public doesn't accept it, it just isn't worth a God-damn."

We made some changes in the proposed Guidelines after the DAC meeting, mainly adding administrative structure. We then set out to acquaint key people and agencies with the details, for NIH supported most but by no means all of the affected research. The widening circle included the National Science Foundation, the Department of Agriculture, other Federal agencies whose authorities were crossed by the NIH Guidelines, the staffs of Congressional committees with jurisdiction over biomedical research, and representatives of industry doing what private research of this sort there was at the time.

ISSUANCE OF THE GUIDELINES

The NIH Guidelines were issued on June 23, 1976. It was front page news, but the reactions were muted. We also established the Office of Recombinant DNA Activities (ORDA), under the direction of William Gartland.

The NIH Guidelines were just that—guidelines, not regulations, which have more of the force of law. The verbs tended to be "shoulds," though some "shall" had been substituted after the February hearing. It was stated that the Guidelines would be frequently revised, but no special procedures for doing so were laid out. They were expected to evolve as understanding of the subject grew. As it turned out, it was not the subject of the Guidelines, but "due process" for changing and administering

¹Office of the Director, NIH (1976-78). Recombinant DNA research, Vols. 1-4 (4,015 pp. in all); for sale by Superintendent of Documents, U.S. Govt. Printing Office, Washington, D.C. 20402, and available in about 600 public libraries of the GPO depository system. (GPO stock no. for Vol. 1, 017-040-00398-6; Vol. 2, 017-040-00422-2; Vol. 3, 017-040-00429-0, and appendix, 017-040-00430-3; and Vol. 4, 017-040-00443-5, and appendix, 017-040-00442-7.) The environmental impact statement, cited in footnote 2, was published as a supplement to Vol. 2 (not included in above page-count).

them, which became the focus for opposition to the research. For the next two and a half years, the Guidelines were to be practically frozen, while the science expanded impatiently within.

EXTENSION OF THE GUIDELINES BEYOND NIH

NIH had no illusions that it was creating guidelines for all the recombinant research in the world. Scientists are citizens of different nations whose laws can supersede intellectual accord. Even within the United States, extension of the same rules to all laboratories could not be achieved by any simple move.

Two different kinds of protest about this incompleteness were brewing in 1976-78. One encouraged extension of the jurisdiction of state and local communities to regulation of laboratory research, a legal area hitherto unexploited. The other sought to persuade DHEW, its Food and Drug Administration (FDA), and other regulatory agencies to use certain narrow authorities to force compliance with common rules. If that failed, the Department was to seek a Federal law to that end. Some fervent advocates of legislation fought for preempting local jurisdictions from enacting more stringent standards if they wished. Others just as vehemently opposed Federal preemption. A Balkanization of recombinant DNA research was one of the most serious and extraordinary threats of this period.

In May 1976 we informed our Department superiors about our intention to issue guidelines, and urged then-Secretary David Mathews to ask the President to direct all relevant Federal agencies to coordinate recombinant DNA activities through an inter-agency committee. Mathews agreed, but no words emanated from the White House. In July, Senators Kennedy and Javits addressed a letter to President Ford advocating the extension of NIH Guidelines to all Federal and private research. Local hearings in Cambridge, Mass.; Ann Arbor, Mich.; San Diego, Calif.; and New York added to a sense of urgency.

The President's letters were finally dispatched in September, and the Federal Inter-agency Committee on Recombinant DNA Research was promptly convened in Bethesda. The research agencies readily agreed to use the NIH Guidelines for the research they supported or conducted. The committee then undertook to examine the regulatory authorities of each of the member agencies and to develop recommendations for possible new legislation. Later the committee would examine patent policy and the international aspects of regulating DNA research.

NEPA AND THE FRIENDS OF THE EARTH

A full discussion of the National Environmental Policy Act (NEPA) with reference to laboratory research in general and to how the NIH Guidelines for recombinant DNA research became involved would fill a volume. NEPA, a law passed in 1969, requires the Federal agencies to determine whether contemplated actions will significantly affect the environment. If so, the action must be heralded by an Environmental Impact Statement (EIS). In the spring of 1976 we were made aware that if we released the Guidelines before issuing an EIS, we could be charged with violating NEPA.

Although an EIS had become common in proposals to level mountains or build dams, the adaptation of NEPA to conjectural hazards of laboratory research was a nightmare. The situation was aggravated by ambiguous and arbitrary procedures for implementing NEPA within DHEW. The tortoise-like march from draft to final EIS could take years.

But delaying the issuance of the Guidelines pending completion of the EIS process was never an alternative. The voluntary agreements made at Asilomar were losing their hold on the scientists, confusion was mounting, and dissidents in various communities threatened to obtain either local regulation or prohibition of the research if Federal standards were not quickly forthcoming. It was obvious that the public interest would be better served--and the opportunity of scientists to continue experiments, better protected--with guidelines than without them, even if an EIS were not published until after their issuance.

We therefore released the Guidelines in June with an announcement that an EIS was to follow. The draft EIS was filed in September 1976, the final one in October 1977.² In May 1977 two suits against NIH were launched in separate Federal courts. One, brought by an organization called The Friends of the Earth, sought to enjoin all recombinant research. The other sought to block the Rowe-Martin risk assessment study. The final EIS was entered as part of the Government's defense in the latter suit (Mack v. Califano). In finding for the Government in March 1978, the Court concluded that NIH, in its EIS, had indeed "taken a hard look" at the consequences of experiments with recombinant DNA. The plaintiff was denied an injunction.

THRUSTS TOWARD LEGISLATION

A bill was introduced in the Senate (S. 621) in February 1977 by Senator Bumpers (D., Ark.), with a companion bill in the House by Rep. Ottinger (D., N.Y.). They were the first of 12 bills to regulate DNA research submitted to the 95th Congress. On February 23, representative scientific leaders were invited to NIH to read selected passages of the proposed new legislation, including heavy penalty provisions. Two weeks later, the last traces of their indifference were dispelled by the acrimonious tone of a forum on "genetic engineering" at the National Academy of Sciences.

The following May the Interagency Committee conveyed to the new HEW Secretary, Joseph A. Califano, Jr., its conclusions that a Federal statute would be required if the Guidelines were to be extended to all recombinant research in the country. It also offered the elements of what it considered an "ideal" law--elements that were quickly converted to an Administration bill introduced by Senator Kennedy (S. 1217) on April 1, 1977. Kennedy then revised the bill radically. In an intensive reaction to this and other proposed laws, scientists and their organizations soon made strong appeals to the Congress. The ardor of the legislators for statutory regulation cooled progressively during 1977-78.

REVISION IS NEEDED

Within six months of their appearance, the NIH Guidelines clearly needed revision. The molecular biologists who had constructed them, if given that chance again, would surely have engaged other disciplines on the route from Asilomar to Bethesda. Especially lacking had been the counsel of experts on infections, who had a better perspective of the improbability that *E. coli* K-12 could be converted into an epidemic pathogen. And more thought should have been given to the containment levels for

²Office of the Director, NIH (1977). National Institutes of Health Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, Part One (147 pp.) and Part Two (appendices, 438 pp.); for sale by Superintendent of Documents, U.S. Govt. Printing Office, Washington, D.C. 20402, and available in about 600 public libraries of the GPO depository system. (GPO stock no. 017-040-001413-3.)

dealing with viral DNA, to the prohibitions, and to the coverage of organisms known to exchange DNA in Nature.

It is also notable that the guidelines constructed at about the same time in the U.S. and the U.K. were quite different in form. The Americans wrote an extensive codification and the British opted for common-law evolution of minimum rules. Both sets, however, were meant to be interpreted and administered centrally, by a GMAG or an ORDA. The U.S. scientists did not want local committees to second-guess their experimental protocols. More comfortable with central decision-making by study sections in Bethesda, they preferred ORDA's interpretations and administration.

But delays in administrative actions were inevitable. The requirement for prior NIH approval of all changes in ongoing projects particularly irked investigators. In rejecting at the start nearly all suggestion of control by their institutions, the scientists had made it difficult to regain a proper balance between local application and national standards.

As a broker between the molecular biologists and the various public interests, NIH also failed to perfect the Guidelines before issuing them. We did not incorporate mechanisms for revision. Discretionary powers to make interpretative judgments and minor changes, essential in so complex and fast-moving a subject, were lacking. There were reasons, however, for avoiding imitation of the formal and formidable procedures of the regulatory agencies. The more we embedded the Guidelines in inflexible administrative molds, the less chance there would be for timely accommodation to the tide of new information that was already rising.

REVISION BEGINS

In January 1977 the RAC commenced to prepare a revised set of Guidelines. A workshop was held in June at Falmouth, Mass., to synthesize old and new information about bacterial host-vector systems. In September the proposed revision--a complete rewriting of the text--was formally presented to me and published in the Federal Register. A two-day hearing was held in December 1977 at which the RAC members defended their proposed changes. Most critics raised questions of process; but some containment levels were severely challenged, and additional meetings of experts on viruses and plant pathogens led to further alterations.

In Departmental clearance, the revised Guidelines encountered more difficulties than the original. Recombinant DNA research had emerged as a scientific issue with immense appeal to laymen, and Secretary Califano's staff took a strong and sophisticated interest in how all relevant law and administrative practices pertained to the new draft. By now, some dissidents and a militant fraction of the environmental movement had also launched a concerted campaign to exact, if science wished to proceed, a more generous tax in procedure.

On July 28, 1978, the proposed revision, accompanied by our environmental impact assessment and a Director's decision paper, was published in the Federal Register. An introductory memorandum from the Secretary invited the public to comment and announced that, after a 60-day period, there would be another hearing chaired by Peter Libassi, the HEW General Counsel.

REVISION COMPLETED

The Libassi hearing took place on September 15 at the HEW headquarters in Washington. NIH staff and I--the "Kitchen RAC"--then dissected the comments received in

testimony and 170 letters, and joined in numerous discussions with Mr. Libassi and his committee. Special meetings were also held with a group of environmentalists who wished to reinforce some of their earlier demands. We also met with representatives of pharmaceutical firms, other Federal research agencies, and members of institutional biosafety committees to discuss their problems with the proposed revisions. A culmination of the Libassi hearings was the reconstitution of the RAC to broaden its public (nonscientific) membership and to combine the technical and policy reviews, usually carried out at NIH in a two-tiered process. The appointment of RAC members was shifted from the NIH Director to the HEW Secretary. The revised Guidelines were released late in December, to become effective on January 2, 1979.

The detailed analysis led by the HEW General Counsel had added a few weeks to the long period of revision. One result was a modest additional burden of procedural safeguards, but this was offset by the removal of any grounds for complaint from the most fervent dissident that the public had not been exhaustively consulted.

There were important achievements in the revision. The new Guidelines contain provisions for continuous and orderly evolution of the rules—even to their eventual elimination when the need passes. Many experiments now judged to be harmless are exempt, and containment for other kinds of experiments has been reduced. Also, the discretion and responsibility for observing the rules are beginning to return to the research institutions, where I believe they belong.

Attempts to enact statutory regulation of recombinant DNA experimentation in the United States need not be revived soon. One hopes they will not, for some of the medieval features of the first bills tended to reappear as later ones passed through the committees. A problem remains, however, in the limits on NIH's ability to protect proprietary data submitted to the RAC. Actions taken by Secretary Califano upon release of the Guidelines, to have regulatory agencies (the Food and Drug Administration, the Environmental Protection Agency, etc.) use their existing authorities to extend the Guidelines over research in the private sector, have been helpful in exploring an alternative to a new law.

MORAL

It is possible that the "recombinant DNA affair" will someday be regarded as a social aberration, with the Guidelines preserved under glass. Even so, we can say the beginnings were honorable. Faced with real questions of theoretical risks, the scientists paused and then decided to proceed with caution. That decision gave rise to dangerous overreaction and exploitation, which gravely obstructed the subsequent course. Uncertainty of risk, however, is a compelling reason for caution. It will occur again in some areas of scientific research, and the initial response must be the same. After that, the lessons learned here should help us through the turbulence that is sure to come.

(This paper was given by W.J. Gartland, Director, Office of Recombinant DNA Activities, NIGMS, Bethesda, Maryland, USA.)

NIH Lecture, May 2, 1979

Introductory Remarks

Good evening, ladies and gentlemen.

I am pleased to welcome you to another NIH Lecture. The first of these lectures was presented in 1953, the year the Clinical Center received its first patients.

Our speaker tonight is Dr. Robert T. Schimke, professor and chairman of the Department of Biological Sciences at Stanford University. His talk is entitled "Gene Amplification and Methotrexate Resistance in Cultured Mammalian Cells." Dr. Schimke will be describing his recent research, which many of you have undoubtedly read about in recent articles by Dr. Schimke and his associates at Stanford.

This work with methotrexate provides the basis for a challenging dialogue about rationales for drug therapy, and establishes the theory that gene amplification may underlie many resistance phenomena of importance in clinical medicine.

Dr. Schimke's contributions to biomedical research have long been familiar to us at the National Institutes of Health. From his early work at the NIH came the recognition that the rate at which a protein is degraded is very important in regulating the concentration of that protein in the cell.

Another interest of Dr. Schimke's has been the mechanism by which steroid hormones influence the expression of specific genes. Using the response of the chicken oviduct to the administration of female sex hormones as a model system, he made fundamental contributions to the theory and techniques of modern molecular biology. He has discovered that the hormone response involves not only an increase in transcription of specific genes, but also changes in the stabilities of the messenger RNAs that they specify.

Dr. Schimke received his M.D. degree in 1958 from the Stanford University School of Medicine. He was an intern and assistant resident in medicine at the Massachusetts General Hospital in Boston before coming to the National Institute of Arthritis, Metabolism, and Digestive Diseases, Laboratory of Biochemical Pharmacology, as a Commissioned Officer in the U.S. Public Health Service.

As many of you recall, Dr. Schimke was here from 1960 to 1966. He became chief of the Section on Biochemical Regulation at the NIAMDD in 1965. After that, he joined the Department of Pharmacology at the Stanford University School of Medicine, and served as chairman of the Department from 1970 to 1973. Since September of 1978, he has been chairman of the Department of Biological Sciences at Stanford University.

Among other professional organizations in which Dr. Schimke is active is the American Society of Biological Chemists. He was recently elected to the Council of this society. He is a member of the National Academy of Sciences and of the National Advisory Council on Aging.

He has received numerous other honors during his career. He was the Maryland Academy of Sciences Outstanding Young Scientist of the year 1964, and in 1969 he received the Charles Pfizer Award in Enzyme Chemistry of the American Chemical Society. He also serves as an associate editor of the Journal of Biological Chemistry.

It is a privilege for me to introduce to you . . . Dr. Robert T. Schimke.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20814

STATEMENT BY

DONALD S. FREDRICKSON, M.D.
DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON

LOW-LEVEL IONIZING RADIATION

BEFORE

THE SUBCOMMITTEE ON ENERGY RESEARCH AND PRODUCTION

AND

THE SUBCOMMITTEE ON NATURAL RESOURCES AND ENVIRONMENT

COMMITTEE ON SCIENCE AND TECHNOLOGY

HOUSE OF REPRESENTATIVES

June 13, 1979

Published in Research on Health
Effects of Radiation, Volume 1,
Part B, Sept. 1980, NIH Pub. No.
81-2196, pp. 1473-1488.

Mr. Chairman and members of the Committee:

This morning I would like to discuss with you the extent and nature of exposure of the U.S. population to ionizing radiation, the contribution of various natural and man-made sources to this exposure, and what we know and do not know about the human health risks from this exposure. As chairman of a newly formed interagency radiation research committee, I would especially like to discuss the organization and conduct of radiation research programs in the Federal Government. Because our view of the future is, at best, clouded, I will confine my remarks to the present.

In order to help answer your questions as thoroughly and accurately as possible, I have asked Dr. Arthur Upton, Director of the National Cancer Institute, and a radiation expert, to accompany me this morning. I have also asked that representatives of the Bureau of Radiological Health of the Food and Drug Administration also be present to provide technical information.

Mr. Chairman, many questions have been raised in recent months concerning the safety of the use of ionizing radiation. Some of those questions concerned incidents related to the United States nuclear weapons testing program, such as the exposure of military personnel in the Smoky and other atomic detonations, and the exposure of civilians in the nearby communities of Nevada and Utah from radioactive fallout from these tests. And recently, of course, the events at Three Mile Island[®] have raised again the whole question of the safety of nuclear power and whether or not the United States should pursue nuclear power as a major source of electricity generation over the next several decades.

Unlike exposure to toxic organic chemicals, which are a phenomenon of the twentieth century, life on this planet has evolved in a sea of radiation since the dawn of time. This natural radiation comes in many forms, in part from the decay of radioactive elements on the earth and in part from high energy particles and electromagnetic radiation from the multitude of nuclear processes occurring in the sun, collectively called cosmic rays. However, in this century, we are beginning to see a significant contribution to human radiation exposure from man-made sources.

Types of ionizing radiation.

The most important form of human radiation exposure is from gamma rays, high energy electromagnetic rays which can be produced either by nuclear reactions or by the bombardment of metallic targets with electrons, the common source of production of x-rays in medical applications. Beta rays or, more accurately, beta particles are electrons emitted from an atomic nucleus which, like gamma rays, may cover a wide range of energies. In general, because most beta particles are less penetrating than gamma rays, they produce less biological damage.

Alpha particles, emitted from the decay of certain heavy atomic nuclei, are charged particles containing two protons and two neutrons. Alpha particles are thousands of times heavier than beta particles and, therefore, do not have the penetrating power of gamma rays or beta particles. Nevertheless, they can be an important source of biological damage if alpha-emitters are deposited within a living organism. A fourth type important in producing human health effects is neutron radiation.

The neutron, emitted in certain types of nuclear reactions, especially in nuclear fission, is moderately heavy but uncharged and thus is quite capable of penetration into biological tissues.

All of these types of radiation or particles are called ionizing radiation. While each is different physically and may come in a variety of energies, they all undergo numerous collisions with matter. The predominant result of these collisions are ions; that is, charged atoms, molecules, and subatomic particles which in turn can interact with the surrounding matter to alter it. This is the predominant source of biological damage from radiation.

However, while ion production results from all such radiation, it is important to make the distinction between different types of ionizing radiation, since the nature of the biological effects produced by each may differ considerably. Gamma rays, and to a lesser extent, beta rays, are considered to be low linear energy transfer (LET) forms of radiation; that is, as each passes through matter, it gives up its energy over relatively long distances. So-called high LET radiation is represented by alpha particles and neutrons, which give up the same amount of energy over much shorter distances. Therefore, the type of damage that each of these kinds of radiation may elicit upon passing through the same type of matter, including biological tissue, would be expected to differ. I shall come back to this in discussing human health risks from radiation.

Radiation measurement.

Radiation is measured in one of two ways. The curie is a measure of quantity of radioactive material and is equal to 2.2×10^{12} disintegrations per minute. Clearly, the amount of energy or amount of ionization

produced by the same number of curies will differ, depending on the particular radioactive isotope that is decaying. Therefore, this is not a particularly useful measure upon which to assess human health effects.

The classic unit of radiation exposure is called the roentgen, named after the discoverer of x-rays. One roentgen is equal to 2.58×10^{-4} coulombs of electrical charge produced per kilogram of air. It is used only for electromagnetic radiation such as gamma rays or x-rays. However, a more useful quantity which has been used over the past two decades is a measure of absorbed dose called the rad, which may be used for all types of radiation, and is equal to 100 ergs of radiation energy absorbed per gram. A more meaningful unit in assessing biological effects is the quality dose equivalent, which is the product of the absorbed dose in rads times the quality factor. This is an empirically derived adjusting factor accounting for the differences in the effectiveness of certain radiation in producing biological damage.

There is clearly some uncertainty in determining what this quality factor is. However, this unit, called the rem, which stands for roentgen equivalent to man, includes for fast neutrons a quality factor of ten, or for alpha particles, a quality factor of one to twenty. This is the high LET radiation. For gamma rays and electrons, the quality factor is approximately one. Therefore, for the latter types of radiation, dose in rads and dose in rems is generally the same, whereas the dose in rads for neutrons and alpha particles will result in a substantially higher equivalent dose if measured in rems.

Practically, in order to determine radiation absorbed, it is necessary to measure these different types of radiation. This is clearly one of the current sources of uncertainty in assessing the radiation exposure and, therefore, the radiation risk to man. Certain types of radiation, such as gamma rays, are relatively easy to measure accurately. However, many of the gamma ray detectors do not measure beta rays. Alpha particles and neutrons are generally more difficult to measure and are, therefore, not usually detected by the normal film badges or ionization chambers.

Alpha particles, however, because they are not penetrating, are difficult to measure but also are usually important biologically only when the emitters of such particles are deposited within the body. And only a select population--those working with fissionable materials or working around particle accelerators--would be exposed to neutrons, which, because they are uncharged, special means must be taken for their measurement.

Population exposure to radiation.

The natural background radiation to which every human being is exposed throughout his or her lifetime is in the vicinity of from about 60 to 140 millirem per year. Approximately half of that comes from cosmic rays and the other half due to rocks, soil, and radioactive decay in the environment and in the human body. There are wide variations, however. The exposure to cosmic rays differs substantially, depending on the altitude at which one lives. When one flies in an airplane at high altitudes, the radiation due to cosmic rays increases considerably. Similarly, the amount of radiation received from rocks and minerals differs substantially, depending on where one lives, whether or not one

lives in a building made of granite or bricks, and whether or not radioactive mineral deposits in the earth have been disturbed and brought to the surface in a particular area. The last century of man's development of technology has contributed, in some cases, significantly to the radiation exposure of individuals. For example, coal, for many years the chief energy source in the civilized world, contains on the average two parts per million of uranium. Coal ash, therefore, contains a substantial quantity of radioactivity. Even natural gas contains polonium, which also increases the radiation level where it is used.

The chief man-made source of radiation is, however, medical and dental x-rays. On the average, this accounts for an annual exposure of about 85 millirem per year per person in the United States. However, unlike background radiation, this varies considerably between individuals. Many receive no exposure from medical x-rays. Yet there is a small percentage of the population--particularly those undergoing extensive diagnoses or radiation treatments--which may receive many rem per year for medical purposes.

It is noteworthy that fallout from past and present nuclear weapons tests conducted in the atmosphere still contribute approximately seven millirem per year to each man, woman, and child living in the United States. The estimates of average exposure to the general population from nuclear power plants currently in operation in the United States and--assuming normal operation--that is, without accidents of significance--is about 0.1 millirem per year per person, although estimates vary. Consumer products, such as television sets, smoke detectors and radium

dial wrist watches, contribute overall less than .1 millirem per year per person. All of these figures represent exposure values averaged over the entire U.S. population. The contribution of each of these sources to a given individual may vary considerably.

Of all the numbers I have quoted you, only that due to natural background—that is, about 100 millirem per year per person—can be predicted with any reasonable degree of certainty in the future. It is not expected, however, that the contribution from the healing arts would rise significantly. In fact, increasing awareness about the potential hazards of ionizing radiation are resulting in much more scrutiny of the equipment used in the medical profession. The Bureau of Radiological Health of the FDA currently operates monitoring programs to reduce excess x-ray exposure. Last year, a set of Presidential guidelines was issued designed to reduce unnecessary exposure to x-rays. Whereas a chest x-ray used to be a routine part of a physical exam for employment, such x-rays are no longer recommended unless there is some medical indication that the procedure would be of benefit to the individual.

The greatest uncertainties in future human radiation exposure clearly lie in the decisions that will be made regarding the development and use of nuclear weapons, nuclear power and consumer products. At present, the contribution to the overall radiation burden from these sources is relatively low compared to natural background, and the bulk of that is from weapons test fallout. However, one would still predict a slight increase in adverse health effects, even from the small contributions due to nuclear power and consumer products.

Adverse human health effects from ionizing radiation

On the basis of the information that has been gained from the study of certain special populations exposed to low-level radiation, the predominant adverse effect of radiation is an increase in the incidence of cancer and of cancer deaths. Each year approximately 400,000 people in the United States die of cancer. ^①How many of those cancers are a direct result of exposure to radiation? Mr. Chairman, science at present is not capable of giving an accurate answer to that question. There have been a number of epidemiological studies on different populations exposed to various doses of radiation and exposed to different types of radiation. ^②Not only do the conclusions differ from study to study, but analyses by different scientists of the same body of data often result in different conclusions.

At several times in the past few years the existing body of data and studies have been analyzed in an attempt to come up with an assessment of human risk from radiation. The National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation, the so-called BEIR Committee, published a report in 1972 and just recently have released a draft report updating their 1972 findings. These questions were also addressed by the UNSCEAR Report (United Nations Scientific Committee on the Effects of Atomic Radiation) in 1977 and by the DHEW-sponsored Interagency Task Force on Ionizing Radiation, which will release its final report in 1979. None of the epidemiological studies, such as that done on the Hanford nuclear workers, the Portsmouth Naval Shipyard submarine reactor workers, leukemia deaths in Utah, and even

[^①Another measure is that 160,000 of each million persons will someday die of this disease.]

[^②See next paragraph for references to analyses of epidemiologic data. Some of the more controversial studies are the following:

I.O.J. Bross, "Leukemia from Low-Level Radiation," *N. Eng. J. Med.* 287:107 (July 20, 1972).

Joseph L. Lyons, M.R. Klauder, J.W. Gardner, K.S. Udall, "Childhood Leukemias Associated with Fallout from Nuclear Testing," *N. Eng. J. Med.*, Feb. 22, 1979, pp. 398-402.

T.F. Mancuso, A. Stewart, and G. Kneale, "Radiation Exposures of Hanford Workers Dying from Cancer and Other Causes," *Health Physics* 33, No. 5, 369 (November 5, 1977).

Thomas Najarian and Theodore Colton, "Mortality from Leukemia and Cancer in Shipyard Nuclear Workers," *The Lancet*, pp. 1013-20, May 13, 1978.

Edward S. Weiss, "Leukemia Mortality in Southwestern Utah: 1950-1964," Vol. II of *Health Effects of Low-Level Radiation*, House Committee on Interstate and Foreign Commerce, U.S. Govt. Printing Office, Apr. 19, 1979, pp. 2204-2218.

the atomic bomb survivors in Japan, is without some measure of uncertainty. Difficulties in accurate dose measurements of each type of radiation, including body burdens, problems in identifying control populations, the identification of confounding variables, and small sample size complicate most of these studies.

Animal data have been collected for a variety of controlled experiments to assess the biological effects of radiation. However, no certain model for the extrapolation of animal risk data to human beings for the various types of ionizing radiation exists. The best data seem to indicate, however, that radiation effects are cumulative, that there is no threshold dose below which there are no biological effects, and that the shape of the extrapolation curve differs between high LET and low LET radiation. While that statement may require some qualification and clarification as we learn more about the repair of radiation damage in human beings, there is not now any compelling evidence for a threshold nor that the dose rate over which radiation is absorbed makes much difference over a wide range of values. However, occupational and population exposure limits and risk estimates are still based on the dose received per year.

Most reports which attempt to assess human risk treat all radiation the same; that is, that a rem is a rem, no matter how it is produced or how or where it is received. Risk is generally estimated over a range of values. The data simply do not allow one to be any more precise than this.

[³See explanation of "LET radiation" on page 335 of these hearings.]

The BEIR report of 1972 predicts a lifetime risk of cancer from a single radiation exposure to be from one to six cancer deaths per 10,000 person-rem of low LET exposure; that is, exposure primarily to gamma rays or x-rays. The 1979 BEIR report gave an estimate in approximately the same range, from about 1 to 3.5 cancer deaths per lifetime per 10,000 person-rem from exposure to low LET ionizing radiation.

Risk estimates for high LET radiation or for specific isotopes deposited in the body, while discussed in the BEIR report, were not estimated due to the lack of exposure data, epidemiological data and reliable risk estimate models. It is generally conceded, however, and there is some evidence to support the contention, that specific isotopes which find their way into specific body organs may, per rem of exposure, produce more serious health effects than the same amount of radiation received from gamma rays or x-rays coming from outside the body. These would include iodine 131, which is deposited in the thyroid gland, particularly in children whose thyroids are much more sensitive to radiation damage, and strontium 90, which replaces calcium in the bone and, therefore, results in the substantial concentration of radiation to the bone marrow cells, producing a higher risk of leukemia than if the same dose were received externally. A concern for those working around reactors or in the processing of fissionable materials is the toxicity of plutonium, a heavy metal alpha emitter, which, once it becomes ingested or lodged in the body, is retained for long periods of time. It is believed that, like most heavy metals, plutonium is concentrated in the liver. It is these types of exposure which are of considerable concern, both from fallout due to nuclear weapons tests,

[*BEIR = National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation.]

from possible nuclear reactor accidents, and for workers involved in milling operations of fissionable materials, both in the weapons industry and for nuclear reactors.

However, the bulk of radiation exposure to the U.S. population is of the low LET type and from external sources; that is, from background radiation or from medical x-rays. While we must continually cite the degree of uncertainty in our knowledge of radiation risk, we may, with the appropriate caveats, apply the range of risk estimates from the BEIR report for low LET radiation to assess the risk of cancer to the population. Taking an average value from the 1979 BEIR report of two fatal cancers per 10,000 person-rem of exposure, one would predict about 4,000 fatal cancers per year from natural background radiation in the United States population. This would account for approximately one percent of all cancer deaths in the United States.⁵ Given the range of values in the BEIR report, this number may be somewhat smaller than 4,000 or it may be somewhat larger. The limits of uncertainty of risk in the 1972 BEIR report result in a range of 2,000 fatal cancers per year to 12,000 fatal cancers per year, or a range of .5 to 3% of all cancers being due to background radiation. It should be mentioned here that some scientists would put the figure considerably above or below this range.

Again, assuming the mean value in the 1979 BEIR report, of two fatal cancers per 10,000 person/rens, the healing arts would result in approximately 3400 fatal cancers per year in the United States population, or approximately an additional 1% of the cancer deaths in the United States. Thus, taken together, the total contribution from both natural

[⁵Committee on the Biological Effects of Ionizing Radiation, "The Effects on Populations of Exposure to Low Levels of Ionizing Radiations," National Academy of Sciences, 1979.]

background and medical radiation, accounting for better than 90% of the total radiation exposure in the United States, we would predict between one and six percent of all cancer deaths due to these sources. By way of comparison, we can estimate that approximately 100,000 cases of fatal cancer per year, or about 25%, are due to cigarette smoking—the only other area in which we have both a large body of data and a very strong adverse effect.

Nuclear power.

Because the assessment of the safety of nuclear power is a matter of particular interest to both of the subcommittees represented here this morning, I would like to take a few minutes to discuss risk estimates from the Three Mile Island accident and to consider nuclear power in general. Three Mile Island is still fresh in everyone's mind. Although we have now become used to the fact that the accident actually did happen, our mood has changed from one of panic to one of taking extra measures to attempt to detect and foresee other problems so that future nuclear accidents can be prevented.

The type of radiation released from Three Mile Island, primarily xenon 133, delivered most of the 3300 estimated person-rem to the population in the form of gamma radiation. There was some additional exposure in the form of beta radiation, which probably was sufficiently weak so as not to penetrate the skin significantly. From the population exposure and risk estimates discussed above, Secretary Califano testified on May 3, 1979, that one would predict approximately one additional case of fatal cancer, one case of nonfatal cancer, and one additional genetic

defect as a result of the accident. The Secretary noted that the addition of these events to the 350,000 expected deaths from cancer among the 2.1 million people living within 50 miles of Three Mile Island, would not be detected.

The exposure to the general population from radiation due to nuclear power is currently estimated to be in the range of one tenth millirem per year per person. Whether this number would increase in the future clearly depends on the course of action nuclear power will take in this country. If the reprocessing of nuclear materials become permitted by law, then this number would probably increase substantially. If the number of nuclear power plants increases, one would also expect an increase.

→ The number of workers at nuclear plants were not included in this exposure estimate, and that will clearly be a function of the number of plants in operation, and the exposures permitted. At present, there are approximately 62,000 nuclear fuel cycle workers who are estimated to receive, on the average, 830 millirem per year, about eight times higher than exposure due to natural background radiation.⁵ Of course, both the worker and population estimates are based upon the assumption that we will not have a serious nuclear accident. We should consider ourselves most fortunate that the release of radiation from the Three Mile Island nuclear plant was not greater than it was, in view of the seriousness of the accident. Had the radiation from the reactor not been contained, our conclusion might have been very different.

This, then, is the current state of the assessment of the biological effects of radiation. Whether or not there will be a proliferation of

nuclear power plants in this country is a decision that will have to be made by Congress and the appropriate agencies of the Federal Government, as will the safety standards designed to protect both workers and the public from radiation exposure, and the approval of plants designed to prevent or greatly lower the possibility of future nuclear accidents.

In order to be sure that we have the best possible information upon which to assess human health risks, the Department of HEW is at present looking into the conduct of all Federal radiation research programs. The rising public concerns over the adverse effects of ionizing radiation have made it very clear that we need better coordination among Federal agencies conducting research in this area. There must not be unnecessary duplication of research efforts between agencies, and there may need to be a change in emphasis to make these research programs more responsive to the public demand to know the risks of exposure to the many forms of ionizing radiation to which the public and certain working populations are subjected.

Under the direction of the President, Secretary Califano convened an interagency group to recommend future policies on radiation research and radiation protection. At the same time, under Congressional mandates, the Department was directed not only to conduct research into the biological effects of radiation, but to see that a review of all Federal research programs in this area was carried out. Therefore, Mr. Chairman, an interagency radiation research committee has been formed, which I chair, which is attempting to address these problems and to develop the sound research strategy for the assessment of the human health risk due

to ionizing radiation. I am confident that through the activities of this Committee, Federal research programs conducted by all of the agencies will be more productive and effective than they have in the past.

That concludes my remarks, Mr. Chairman. My colleagues and I will be happy to answer any further questions the Committee may have.

CANCEP MORTALITY AMONG BLACK AMERICANS

HEARING
BEFORE THE
SUBCOMMITTEE ON
HEALTH AND THE ENVIRONMENT
OF THE
COMMITTEE ON
INTERSTATE AND FOREIGN COMMERCE
HOUSE OF REPRESENTATIVES
NINETY-SIXTH CONGRESS
FIRST SESSION
ON
HIGH MORTALITY RATE FOR CANCER AMONG BLACK
AMERICANS AND LATE DIAGNOSES WHEN CANCER HAS
REACHED AN INCURABLE STATE

JUNE 18, 1979

Serial No. 96-22



Printed for the use of the
Committee on Interstate and Foreign Commerce

U.S. GOVERNMENT PRINTING OFFICE

WASHINGTON : 1979

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CANCER MORTALITY AMONG BLACK AMERICANS

MONDAY, JUNE 18, 1979

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2318, Rayburn House Office Building, Hon. Henry A. Waxman, chairman, presiding.

Mr. WAXMAN. The subcommittee will be in order.

The American health system can deliver the very finest care in the world. Our medical technology and the education and training of our physicians and other medical personnel are second to none.

To assure that our citizens receive the full benefit of our health care system, major Federal financing for health care began in 1965 with the enactment of medicare and medicaid. These two programs were directed at two segments of our population believed to suffer the most inequities in gaining access to health care—the elderly and the poor.

Today's hearing on the high rate of cancer mortality among black Americans is an important case study of gaps that still exist in our health care system, despite enactment of medicare and medicaid. The subcommittee will investigate today the chief reason for the high mortality rate from cancer among black Americans—late diagnoses when cancer has reached an incurable stage.

This morning we will hear testimony indicating that for many black Americans and other minorities, the local emergency room has replaced the family doctor. Medicaid guarantees access to emergency care but medicare and many State medicaid programs do not offer diagnostic care and annual physicals, the type of screening that detects cancer at an early and treatable stage.

America is the richest Nation on Earth. Yet in the Nation's Capital of Washington, D.C., today black males have a 60 percent greater risk of dying of cancer than white males. It is important that this subcommittee, which has a demanding legislative agenda, never lose sight of the larger picture. It is essential for us to look at our health care system as a whole to find out who is falling through the cracks of that system and why.

Is our Federal reimbursement skewing health services for costly treatment of illness rather than prevention and early diagnosis of disease? That is the question our hearing on the high mortality rate among black Americans will attempt to answer today.

STATEMENT OF DONALD S. FREDRICKSON, M.D., DIRECTOR,
NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE,
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
ACCOMPANIED BY JOSEPH F. FRAUMENI, JR., M.D., CHIEF,
EPIDEMIOLOGY BRANCH, NATIONAL CANCER INSTITUTE,
AND EARL F. POLLACK, PH. D., CHIEF, BIOMETRY BRANCH

Dr. FREDRICKSON. It is a pleasure to appear before the subcommittee. I think you have picked a very perplexing and extremely important public health issue for discussion this morning. That is the disparity which exists between the black and white populations of this country with respect to cancer incidence and is even more striking with regard to cancer mortality.

In comparing statistics, several aspects are noteworthy. Overall, cancer among black males is higher than for any other race or sex group. At the same time, black females have less cancer than either white females or males. However, as has already been stressed today, cancer mortality rates in both sexes are greater among blacks than among white, with excessive rates starting in 1950 for females and 1956 for males.

Also striking is the comparison of survival in black and white cancer patients. On the average, blacks live for a substantially shorter period than whites after diagnosis of cancer has been established.

While it is possible to make a few generalizations about these data, it is important that we examine the figures very carefully. Not only do the cancers at different sites show very different patterns between blacks and whites, but there are also some important differences between males and females.

It is generally believed that the differences in cancer incidence and death rates between blacks and whites are due largely to environmental and socioeconomic factors rather than to intrinsic differences between the races, although there are some important exceptions. For example, there are differences in the pattern of leukemia among black and white children. But in the main, I think that most important factors responsible for these differences are not genetic but environmental or socioeconomic.

A greater percentage of blacks than whites live in urban areas. The incidence and mortality rates for all forms of cancer, regardless of race, are higher in crowded industrialized urban areas than they are in the rural sections of the country.

Other risk factors for cancer which have to be considered are cigarette smoking, alcohol use and abuse, diet and exposure to occupational and environmental carcinogens. On the whole, but not necessarily in every instance, these risk factors are suggested to be more important and more prevalent among the black population.

A major reason for the difference in mortality rates between blacks and whites is attributed to the stage at which cancer is detected. For example, less affluent socioeconomic groups tend to use medical services mainly in acute situations rather than for routine medical care. This diminishes the likelihood that cancer will be detected while it is still localized.

Among other factors to consider, one may note that mortality rates can be influenced by concomitant illness. Overall, if one population group is less healthy than another, the less healthy

may respond to a given disease less successfully. However, even when quality of medical care and stage at which cancer is diagnosed are taken into account, survival for blacks is still poorer than for whites.

The observation of higher mortality in blacks is not restricted merely to cancers. If one looks at other major diseases, one finds that mortality rates are generally higher for blacks than for whites. Many of the same socioeconomic and environmental factors that contribute to the mortality rates for cancer, such as stress and diet, contribute to other major diseases as well. Mortality from all major cardiovascular diseases is 30 percent higher for blacks than whites. Proportionately more blacks—22.2 percent—than whites—15 percent—currently have hypertension, a major risk factor for heart disease. This pattern was evident for each age group except for those aged 17 to 24 years. The incidence rate for diabetes is also significantly higher for black females than for whites of both sexes and the mortality ratio for diabetes is more than twice as high for blacks as it is for whites.

Let us turn now to incidence rates for certain specific cancers. In general, the most common cancers among U.S. blacks are prevalent also in U.S. whites but are relatively uncommon in black populations of Africa, suggesting the importance of environmental factors. Colon cancer, for example, is rare in Africa. In the United States the incidence, while higher in whites than blacks, is rising rapidly in blacks. This may be attributed in part to an increase in the ratio of fat to fiber in the diet of black people as they become more urban and affluent. The incidence of cancers of the lung and larynx are higher in U.S. blacks than whites, while the occurrence of these cancers is very low in Africa. The differences between continents are attributed primarily to cigarette smoking and occupational exposure.

Pancreatic cancer is also smoking related and occurs more often in blacks than in whites. It is suspected that occupational exposure and dietary factors may also play some role. The incidence of esophageal cancer is much more common in blacks, particularly black males. This is a disease which appears to be related both to smoking and excessive alcohol consumption. That is, smokers who also drink heavily are far more prone to cancer of the esophagus than those who do not. The incidence rate for cancer of the prostate is also higher in blacks than in whites but we do not know why that is so. When a Howard University study compared black men in the District of Columbia with those in Nigeria, it was found that the risk of occult or in situ type of prostate cancer is just about the same in both populations. However, clinical or invasive prostate cancer is far more common in the District of Columbia than in Africa, suggesting the activity of environmental factors that may promote the growth of this cancer.

As I mentioned previously, there are differences in cancer incidence for which no direct environmental link has been established. For example, in black women the incidence rates for cancers of the esophagus, stomach, and pancreas, as in black males, are higher than they are in whites. Cancer of the cervix is also more common in blacks than in whites but is decreasing rapidly. The prevalence of cancers of the breast, uterine corpus, and ovaries remain lower

in black females than in white females. Because breast cancer and uterine cancer form a large fraction of cancer in females, it is thus possible to explain why the overall incidence of cancer is 6 percent lower in black women than it is in white women.

There are a few types of cancer that are very rare in blacks compared to whites, for example, testicular cancer and Ewing's sarcoma of the bone. In addition, the peak of acute lymphocytic leukemia which occurs in white children at ages 3 to 4 is a phenomenon not seen in black children. The incidence of skin cancer, particularly malignant melanoma, is also many times lower in blacks than it is in whites. On the other hand, multiple myeloma occurs more frequently in blacks and at an earlier age than in whites.

An analysis of the incidence data from the third national cancer survey, 1969-71, was carried out in an attempt to determine the differences in cancer incidence between black and white populations. When an adjustment for income and education was made, the excess risk of lung cancer among black males disappeared and the relative risks for cancer of the cervix and for cancer of the esophagus for both males and females were reduced considerably. For some other sites, such as prostate cancer and multiple myeloma, the adjustment had little effect, suggesting that the excess risk of certain cancers among blacks cannot be explained by differences in socioeconomic status.

How much of this racial disparity might be accounted for in the quality of medical care available to blacks or to whites? While this factor cannot easily explain the excess incidence of cancer in blacks, it is believed to contribute to the poorer survival and higher mortality rates.

In summary, studies have shown that there are overall differences both in incidence and mortality rates between blacks and whites. In general, cancer mortality rates are higher for blacks than for whites. Links have been established or are strongly implicated between high rates of cancer and urban living, certain occupational hazards, smoking and alcohol consumption, socioeconomic status and years of education. Some of these links may explain the cancer incidence differences between black and white populations. However, there are a small number of cancers for which none of these associations exist and which one can only attribute to genetic factors. These would include cancers that are prevalent only in whites or in blacks or where the natural history of the disease is very different between blacks and whites.

I shall anticipate your question, Mr. Chairman, as to what the National Institutes of Health is doing to elucidate the differences in cancer incidence and mortality rates between the black and white populations and what we are doing to educate the black population in how it may reduce its preferential risk from many forms of cancer. The National Cancer Institute is engaged in efforts to distribute informational and educational materials to minorities. This is done in cooperation with organizations which serve minority populations. The Office of Cancer Communications has specifically worked with groups which serve the black population, including the National Association of Community Health Centers, the National Medical Association and the National Black Network.

These efforts have included the publication of a handbook to aid Cancer Information Services, as well as other NCI publications provided free to community health centers and affiliated organizations. NCI has developed a series of public health service ads targeted at black audiences through newsletters and other media, placed stories on cancer among blacks in *Ebony* and *The Black Collegian* and produced a special publication, "What Black Americans should Know About Cancer."

In addition, Mr. Chairman, we are conducting and supporting ongoing epidemiological studies around the country relating to the black population. NCI is presently collaborating with medical schools and hospitals to study cancer of the esophagus among blacks in the District of Columbia to try to learn why the rates of this form of cancer are higher there than in other urban areas. There are also studies now underway in Los Angeles looking at both esophageal and prostatic cancers and another in New Orleans investigating lung, pancreas and stomach cancers.

I should point out that the early epidemiology work elucidating the differences in black and white populations was conducted or sponsored by the National Cancer Institute. In fact, NCI has conducted one of the most extensive epidemiological surveys of the distribution of cancer by race in the United States that has ever been done and has published a volume of cancer maps to help stimulate further work.

In addition to our education and information programs and epidemiological studies, what else can be done? Clearly, Mr. Chairman, more needs to be done. We believe that as our research and training programs expand, the increased opportunities for minorities and blacks will make also an important difference in the amount and type of information that we are likely to obtain concerning these differences between the races. I think that here we have an example of why it is extremely important that we maintain an increased effort to draw more blacks and other minorities into the mainstream of current research. For problems like these, these serious epidemiological differences between people will not be given attention except when people of those ethnic groups themselves are involved and have a major role in designing and carrying out such a program.

That concludes my testimony, Mr. Chairman. I will be happy to answer any further questions that you may have.

Mr. WAXMAN. Thank you very much.

Mr. LELAND. I appreciate your testimony and I would like to ask you this: I am curious about the problem or the difference between black women and black men and the incidence of cancer. That is among them. Can you answer that question?

Dr. FREDRICKSON. Why black women have less cancer than white men?

Mr. LELAND. Why they have less cancer than black men.

Dr. FREDRICKSON. Than black men? Well, we are not entirely certain why this is true, Mr. Leland. If we leave out the cancers that are exclusively female or practically so, such as breast, the body of the uterus and ovary, let us look at some differences in the incidence rates between black women and black men.

**VETERANS' CLAIMS FOR DISABILITIES FROM
NUCLEAR WEAPONS TESTING**

**HEARING
BEFORE THE
COMMITTEE ON VETERANS' AFFAIRS
UNITED STATES SENATE
NINETY-SIXTH CONGRESS
FIRST SESSION**

WEDNESDAY, JUNE 20, 1979

Printed for the use of the Committee on Veterans' Affairs



**U.S. GOVERNMENT PRINTING OFFICE
WASHINGTON : 1979**

Published in Research on Health
Effects of Radiation, Volume 1,
Part B, Sept. 1980, NIH Pub. No.
81-2196, pp. 1522-1526.

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TESTIMONY OF A PANEL CONSISTING OF: DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH; DR. CLARK HEATH, JR., DIRECTOR, CHRONIC DISEASES DIVISION, BUREAU OF EPIDEMIOLOGY, CENTER FOR DISEASE CONTROL, ATLANTA, GA., ACCOMPANIED BY DR. GLYN CALDWELL, CHIEF, CANCER BRANCH; AND SEYMOUR JABLON, STAFF DIRECTOR, MEDICAL FOLLOW-UP AGENCY, NATIONAL ACADEMY OF SCIENCES, NATIONAL RESEARCH COUNCIL, WASHINGTON, D.C.

Dr. FREDRICKSON. Mr. Chairman, I am Dr. Fredrickson. I have a statement of approximately four pages and I shall abbreviate that in the interest of time, if you would like.

Senator SIMPSON. Thank you very much.

Dr. FREDRICKSON. I am here representing the National Institutes of Health and as such, I presume I am one of those asked to comment on the human health effects of ionizing radiation, more particularly on its causation of cancer.

I must say, Mr. Chairman, that to the extent that current compensation systems and traditional tort law are always tied to trying to trace injury to a demonstrable cause, modern medical science cannot be as helpful as it would like to all of the people who have an interest in this hearing today.

There is no question but that radiation can cause cancer. We know that from studies of individuals exposed to high levels of radiation. We believe this to be true for low levels of radiation as well as has been reiterated today. The general belief is that there can be no threshold of safety for any exposure to ionizing radiation.

PREPARED STATEMENT BY DONALD S. FREDRICKSON, M.D., DIRECTOR, NATIONAL
INSTITUTES OF HEALTH
HEALTH EFFECTS OF LOW-LEVEL IONIZING RADIATION

Mr. Chairman and Members of the Committee:

This morning you have asked that I comment generally on the human health effects of ionizing radiation, more particularly on its causation of cancer, and most specifically on the relationship between exposure to radiation during the testing of nuclear weapons and the subsequent development of cancer.

To the extent, Mr. Chairman, that current compensation systems and tort law are based on injury always being tied to a demonstrable cause, modern medical science cannot be nearly as helpful as it would like to be to the parties involved in this morning's debate.

Cancer is a group of diseases having complex and multiple causes, exposure to radiation being only one of them. At present we can assign a specific or nearly unique cause to only one or two rare kinds of cancer. The vast number of cancers--which account for 16 percent of deaths in this country--are of multiple and usually undetermined cause.

In many other kinds of disease or injury, specific signs or test results point to specific cause during life, or revealing traces after death make possible certain assignment of cause. Most causes of cancer, however, show no such cooperation; the lesions are the same when due to one cause or another and bear no witness to their specific origin.

Moreover, the chain of events which result in the induction and development of cancer often begins two or three decades earlier than the appearance of the disease. People are exposed to multiple carcinogens and co-carcinogens throughout their lives. Some of these will directly cause the initial damage to the genes that may be the first event in the cancer. Others may have to undergo transformation in the body by other

chemical reactions or be influenced by certain promoters before the damage is done to cell control mechanisms. The individual's ability to repair this damage or later to reject or control malignant cell growth will determine relative susceptibility to development of cancer. Several carcinogenic influences may be much more serious than any one alone. Smoking, for example, greatly aggravates the ability of asbestos to cause lung cancer.

Radiation can cause cancer. We know this from following populations exposed to high levels of radiation or experimental animals. Exposure to radiation may be the most important event in the induction of cancer in a relatively few individuals. It may contribute, along with other carcinogens or co-carcinogens, to a large fraction of cancers. Exposure to radiation increases the risk for all types of cancer. Cancers in a few sites appear to be significantly more prone to develop after radiation than cancers at other sites.

As I have indicated earlier, we are presently unable to determine precisely the net contribution of each of many carcinogenic stimuli to which a given cancer patient has been exposed. The best that we can do is to attempt an assessment of the probability that radiation may have increased that individual's chances of getting cancer. Several things are helpful here. The history of exposure, including the kind of radiation and the dose must be considered. The time of the onset of the disease in relationship to the exposure to radiation is also sometimes helpful. And, it is necessary to learn all possible about the exposure of that person to other known carcinogens.

In a given patient with cancer, then, Mr. Chairman, any unusual exposure to radiation must compete with any number of confounding variables as the cause of the disease. We also know that every person in the world is constantly exposed to natural background radiation from a variety of sources. Many will receive further exposure from medical and dental x-rays. These two sources are estimated to account for from 2 to 10 percent of all cancers in the United States. In comparison, the National Cancer Institute estimates that about 25 percent of cancer is related to cigarette smoking.

To be sure, Mr. Chairman, our difficulties in estimating the probability of radiation contributing to an increased risk of cancer is compounded by several remaining problems: the uncertainties regarding the extrapolation of high dose radiation exposure to cancer risk at low doses, poor or incomplete records concerning the conditions surrounding radiation exposure, and a lack of data concerning exposure to other agents over the previous decades which may have contributed to cancer.

In conclusion, continuing research will undoubtedly improve our ability to determine accurately the human health risks of exposure to different types of ionizing radiation at varying dose rates. An inter-agency radiation research committee, which I chair, has embarked on an attempt to develop a better Federal research strategy concerning this important problem.

Other aspects of the problem of improving comprehensive record-keeping and establishing the medical records of each individual have been subject to study and recommendations by the recent Interagency Task Force on Radiation. However, I must emphasize, Mr. Chairman, that even as we acquire more precise knowledge about the role of radiation in cancer

induction and obtain more accurate and complete records of exposure to radiation and other carcinogens, it may never be possible to assign to each case of cancer the degree to which radiation contributed to its cause.

That concludes my remarks, Mr. Chairman. I will be happy to try to answer any questions you may have.

OPENING REMARKS 1/

by

Donald S. Fredrickson, M.D.2/

I am particularly pleased to be here this evening at this International Workshop on Slow Virus Infections of the nervous system. As you know, much of the seminal work in slow virus research has been done by our own NIH scientists, and this workshop, together with the formal opening of our new laboratory in Frederick, Maryland, marks an exciting sequel to the award, two years ago, of the Nobel Prize to Dr. Carleton Gajdusek for his work in this field.

It is very fitting that we are here at the Department of State, because of the particularly international character of this research. In fact, slow virus research is a prime example of the importance of worldwide collaboration in science. The work on such disease in man began with the discovery of kuru in New Guinea; but that work made use of much pioneering research on similar infections in animals, carried out in several countries by a number of scientists--many of whom we have as our guests this evening.

No one can do justice to an occasion like this, and the simple fact of Gajdusek and Gibbs' demonstration that some forms

1/ Delivered at the International Workshop on Slow Virus Infections, Diplomatic Suite, Department of State, Washington, D.C., on July 31, 1979

2/ Director, National Institutes of Health, Bethesda, Maryland

of pre-senile and senile dementia are slow infections caused by viruses, speaks for itself.

The potential of this work is enormous. We are confident of identifying, within the next few years, the causes of a whole spectrum of chronic degenerative neurologic disorders--including multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, and the other dementias. There may well be the possibility of delaying the onset of early aging in man.

We expect that it will not be too long before there can be another International Workshop on Slow Virus Infections. We hope very much that all of you can be with us then.

REMARKS 1/Donald S. Fredrickson, M.D. 2/

DR. FREDRICKSON: Thank you, Mr. Chairman. I wanted to make myself available for questions, primarily, but since I'm here, I will have the foolishness to make one or two comments relative to what little of the hearings I have heard this morning and particularly the briefs that I was privileged to read yesterday.

I realize that I am at risk of being boring or even worse, like Truman would have been if he had to come himself to argue Youngstown Sheet and Tube vs. Sawyer in 1952 instead of sending a real lawyer. The first is one that I sense from reading the briefs, although I think that it is not as strong as I was afraid it might be, having listened to the comments of the Board; and that is a misapprehension that we are interesting in trying here to correct concerns that many of us have about the impact of the Freedom of Information Act on scientists' proprietary rights and the scientific process in general. That is not so. We are concerned with only seeking some discussion of possible relief for two very specific instances, that of the clinical trial and the epidemiologic study.

Clearly, all of these other issues are not subjects that we regard as appropriate for the Board to necessarily concern themselves with at this time. A great deal of the content of some of the briefs that I read were directed toward these other issues which were part of the introduction to the NIH position.

1/ Testimony before the Secretary's Ethics Advisory Board, Friday, September 14, 1979, Hubert Humphrey Building, Room 800.

2/ Director, National Institutes of Health, Bethesda, Maryland

But I must say that I still regard as very important the question of protecting the rights of individuals to participate and to continue to participate in clinical trials after they have entered them under the appropriate requirements for fully informed and knowledgeable informed consent, and who agree to take a considerable risk in some instances, and in nearly every one, undergo a great deal of inconvenience to participate. This very narrow question still bothers me, and I regard it as one having high ethical content. I am pleased to note that Dr. Fried in his brief believed there is an ethical issue here for the Board and I believe it, as well.

The question I would deliberately pose is in that very narrow frame, as opposed to the question of government investment, or the loss of information to society necessarily. Do not those who have begun to participate in a clinical trial have a right to continue without disruption or perturbation or destruction of the trial because of a premature release of a very specific kind of data -- the trend data -- in ways that might so alter the behavior of the participants that the premises on which the hypothesis is being tested is based or altered such as to make the trial impossible to continue?

The ethical issue that lies in the question of protecting similar kinds of data in epidemiologic studies certainly seems to me less related to the individuals who are actually the source of the data. Here it broadens out into something more of a social/political question as to how much right does society have to know the truth or the reality as it is sought in such a trial where, again,

premature release of the data might so perturb the source of information that that reality might become possible to learn.

Nevertheless, I still believe after reading the briefs and hearing the discussion this morning that there are ethical issues involved in the application of the Freedom of Information Act to these two specific examples of scientific experimentation, issues about which we had expressed earlier to the Board our concern.

CHAIRMAN GAITHER: Is your concern a broad one in relating to the trials that must end because of the premature publicity, or are you really just concerned about a trial which is the only real hope of getting some important information?

It seems to me you have implied that that's really your concern in the past but you've never said it. And it's one thing to urge a change in the Freedom of Information Act because of budgetary questions, great expenditure, great inconvenience; it's quite another to urge that change because you are disrupting a trial that provides the only real hope of getting some meaningful information that we need if we are really to inform the public.

DR. FREDRICKSON: I don't believe, Mr. Chairman, that we should engage in clinical investigation, at least in the order of magnitude of the kind of trial we're talking about, unless it does represent the only real practical way of getting an answer to an important question, a question that has significance and importance to the subjects and, perhaps, to others like them who are not participating.

So that in that sense, I am talking about the process that appears to be the only way to get an answer, one that is of sufficient

importance to ask people, through an informed consent process, to participate and to continue to participate under circumstances that should allow us to derive an answer to the hypothesis under test.

I think something Mr. Halpern said merits comment here, and that is, that he's quite right. One can manipulate the nature of trials so that the beginning may be clear but the end may not. I think that one should not engage in a major clinical investigation unless it's quite clearly agreed that there is an end and that that end point is well enough defined so that it cannot be distorted or indefinitely protracted.

Does that answer your question?

CHAIRMAN GAITHER: In part. If one were to assume that your belief in terms of when clinical trials should be conducted, in fact, reflects reality as to when they are, in fact, conducted. Is it your judgment that those criteria have governed at least Federal funding of clinical trials in the past?

DR. FREDRICKSON: Well, I think that in recent years they have become more and more the determining factor. These trials become more and more expensive, more difficult to do, and I think that, while we have in the past entered upon clinical trials that were insufficiently designed, we have now learned by trial and error -- and we have been constrained by the realities of marshalling resources -- to not engage in a major trial until, yes, they are the only means of getting an important answer to such a question.

DR. TOSTESON: Just to press on that a little further to make sure that we understand your position; Mr. Halpern raised the question

about what is special about scientific information that should make it deserving of different treatment under the law than other kinds of information.

If I heard you, you said that NIH would seek exemption for clinical trials and for epidemiologic studies involving human subjects in which the disclosure of information before completion of the study would imperil the goals of the study. I'd like to know whether that is a correct understanding of your position of the restriction in the area of scientific information where an exemption would be justified, and I'd also like to know whether the exemption should be such as to permit discussion or whether it should be absolute.

What concerns me here is that I can well imagine some instances in which you'd want to interrupt a study because it became so clear that the risk was enormous.

DR. FREDRICKSON: Well, the answer to your first question is, yes, we would like to be very restrictive in seeking any kind of protection or exemption from the Freedom of Information Act for the studies of the kind that you described. I think that it's important that we place into the record the fact that many of these trials are interrupted prematurely, and they are deliberately done so because it's determined that either there will be no meaningful end point achieved, or it is clear that we've already reached the end long before the projected time, or that unforeseen events have arisen that place the subjects in hazard.

So, clearly, that opportunity, that necessity, of interrupting trials prematurely on that basis would still remain.

MR. LAZARUS: Once a trial is completed, do you have any objection at all to making the information available to the public?

DR. FREDRICKSON: No, I do not. I would like to qualify that, however. It is difficult sometimes to know when a trial is completed. I don't want that to seem paradoxical after what I have said earlier. But it may take a long time for a definitive analysis of data to be completed. Clearly, there must be protection built in so that this period is not protracted unduly. Sometimes it is difficult to determine exactly when you are finished with all the data, but basically, I have no great trouble with making sure that all these data become available at an appropriate and reasonably early time after the completion of a study.

MR. LAZARUS: You are looking for a postponement of a disclosure, rather than withholding this disclosure?

DR. FREDRICKSON: Absolutely, because I think seeing an absolute proscription on a disclosure would be quite the antithesis of what we are really seeking to do and to protect here. I should say, to round out my discussion, that I began with one weakness in the NIH position, and I want also to admit the second, which I think is very important. Reference has already been made to it today. A second weakness in our argument, in our proposition, is the fact that we do not have concrete evidence or have not yet presented to you evidence that if we don't get the relief which we have suggested we should, there will be destruction on the scale that we have suggested.

And I think this is a very important point the Committee will have to consider. But I think that we should be pressed, indeed, to try to present as many arguments as we can to back up our presumption of disaster.

It's interesting that all the Federal agencies that conduct biomedical research which meet in a FCCSET Health and Medicine Committee, of which I am the Chairman, have recently discussed this subject. I think that all agencies, without exception, have expressed the same alarm that NIH has expressed. And yet, none of them have any more in the way of antidotes or proof of disaster to offer than do we.

DR. FOSTER: One question, Dr. Fredrickson.

Completing a study, how does that impact on interim reports that may be built into the research design? Up front, what would be the position of releasing interim reports?

DR. FREDRICKSON: Well, I think the release of interim reports is perfectly appropriate. We're really seeking, again, I would emphasize, to protect only the narrowest kind of data and that is trend data which are not statistically significant, subject to misinterpretation or exploitation in ways that would distort the completion of the study as normally planned.

Other interim reports of how many participants there are or other such information judged either to be not in a category I described or certainly of importance to the subjects who are participating should not be protected by any kind of exemption. That is not the purpose of this at all.

CHAIRMAN GAITHER: Father McCormick.

FATHER MCCORMICK: I'd like to get our experts confronting one another. Therefore, let me ask this question. What is your reaction to Mr. Halpern's statement that the facts against the strong presumption are not there. The case has not been made there for an exemption.

DR. FREDRICKSON: It depends, Father McCormick, upon how much proof you want or how much evidence you require to come to some decision about whether the action is necessary or not. Some of us have a premonition that all of the ingredients are there for the losses that we say will occur, if premature information is mishandled in relation to a trial.

I believe that what we are seeking to do is so much in the interest of the individuals who participate in these trials, and who are also members of the public. The stake of the public in the appropriate outcome of these trials is such that I would act without that evidence, because I cannot see that it in itself really does represent the degree of harmful intervention in the status of the Freedom of Information Act that others see it to be.

It is, of course, for that reason that I would again emphasize that, although it is difficult, the exemption, as we see it, should be a very narrow one.

CHAIRMAN GAITHER: Dr. Henderson.

DR. HENDERSON: I wonder if I might ask you to respond to Mr. Halpern's hypothetical case that he raised in regard to the situation of St. Elizabeth Hospital, and he is representing a group

in a class action suit participating in one of the trials, and some of them were experiencing adverse results. I'm not sure you were here when he presented this. His statement was, as I recall it, that he did express concern that if this exemption were granted, this would seriously impact any action that might be taken on behalf of the patients.

I wonder if you would respond to that in terms of present protections that they have, irrespective of if this worked.

DR. FREDRICKSON: I didn't hear his scenario relative to St. Elizabeths, but if the question is, would we be preventing patients from having appropriate attention to untoward reactions by seeking this prevention of disclosure in a premature way, most certainly I should think not. Because these studies are designed to protect the individuals and to provide a base for interpretation of unforeseen events. That is the job of the Safety and Monitoring Boards, to be made aware of untoward reactions, unanticipated results, and to deal with them. And to deal with them as the patients' adversary, and not as an agent of the government for protecting some higher right of society.

I think the patient's right must come first. And that is the primary reason why the Safety Boards are there.

DR. HENDERSON. I think he was supposing or assuming from this that the patients would not have resources, I guess, to any compensation or would not have access to possible knowledge of therapies they would have received or might have received under the trial.

DR. FREDRICKSON: Oh, I think that's absolutely untrue because we are talking about prolonging disclosure, not preventing it, not burying for any unnecessary time after the end of the trial any of the relevant facts that pertain to the individuals or to the scientific experiment in its entirety. We are not seeking to do that. I think that would be wrong.

CHAIRMAN GAITHER: Mr. Conway?

MR. CONWAY: My concern goes to the question of have you exhausted your other remedies before resorting to amending the Freedom of Information Act. In other words, have these two problems been taken to the appropriate authorizing committees of the Congress that normally deal with the Center for Communicable Diseases' programs and the NIH programs, so that the kind of cross-cutting deliberation could take place on these two problem areas prior to an effort to amend the Freedom of Information Act?

DR. FREDRICKSON: We have not discussed these issues, in any detail at all, with any of our appropriations or authorizing committees. They are not the committees that would actually have jurisdiction over changing the Freedom of Information Act.

MR. CONWAY: I know that. But I mean a more careful definition of the way the CDC operates with respect to the handling of information and exploration of the problems and a more careful definition, and maybe even statutory action on the part of Congress could be formulated in such a way that it would be respected within the framework of the Freedom of Information Act. That is an approach that I am asking whether there has been any thought given to pursuing it.

DR. FREDRICKSON: We have not done so and it is the general perception of those who advise us about changing statutes that this probably would not be a very productive approach, to step into the terrain of the committees that are responsible for this legislation.

I think it should be said that what Charles Halpern says is true. Since 1974 there's been a lot of discussion about the Freedom of Information Act. I'm unaware, however, that at any time this has been brought before the Congress, this matter of the very narrow jeopardy that we are talking about here and I feel it fairly certain that when the authors of that Act promulgated it, and when it was discussed by the Congress, nobody ever thought of its conceivable implication on this aspect of biomedical research.

CHAIRMAN GAITHER: Mr. Halpern, you had a question you'd like to ask?

PROF. HALPERN: I have one I think is particularly important to the Committee and to the revision of my paper, and that is, your characterization of the data that you would like to see shielded by an amendment. The characterization in the Federal Register is really quite broad, "Data from clinical trials and observation from epidemiological studies."

Did I understand you to suggest it is only some of the data drawn from those studies that should be shielded by an amendment and not all the data, and also, that it was only major trials? I thought you made a distinction between major trials and other trials. Am I correct about that? I think it would be helpful to the Committee and

certainly to me to be as clear as possible about what the scope of your proposal is.

DR. FREDRICKSON: Yes, in answer to your first question, it's very clear that we have failed to provide an adequate definition of the kinds of data for which we would seek some protection or postponement of disclosure. All information from clinical trials, major or minor, of course, we would not wish to protect. In fact, we seek to make this as widely known to the public as we can--that is, the number of participants, the questions being asked, the costs and cities. Everything but the privacy of the individuals who are actively participating. Only those data which bear upon the continuous participation of those who are in the study, in turn depending upon exactly the premises that one wishes to test and which variables one is trying to control, are the subject of our petition here.

PROF. HALPERN: In other words, the mere fact that disclosure of some data might mislead the public would not be a justification for withholding the data?

DR. FREDRICKSON: That's a tricky question.

PROF. HALPERN: I don't mean it to be.

CHAIRMAN GAITHER: You are saying not that factor alone, that factor alone is not enough.

DR. FREDRICKSON: I think we are not seeking to mislead the public in any way in trying to protect the status. Is that what you asked?

PROF. HALPERN: No. Suppose you have a piece of information growing out of a clinical trial. Disclosure of that data could not possibly jeopardize the participation of the experimental subjects or the continuation of the trial. But it would or could have the effect of misleading some significant elements of the public. Would you like an exemption that would under those circumstances give you discretion to withhold that piece of information?

DR. FREDRICKSON: Let me answer in this way, that I believe we would only be interested in protecting those data that would mislead that portion of the public participating in the trials, although it might extend beyond that. I am sure it would in many instances.

I cannot imagine immediately information that would mislead other members of the public who were not participants, but I suppose it is possible. I should have to think about your question. I think it doubtless is something that I really need to explore.

PROF. HALPERN: I really don't mean it as a trick question, but I think it is an important distinction.

The other question that I asked was whether you would like an exemption that applied to all of your research activities or only to major studies.

DR. FREDRICKSON: Well, there we fail to make adequate definition of what is "major." Many clinical trials, so-called first phase, involve only a few people. And here there really is very little at issue. It is primarily for the major trials involving a larger number of people. But, again, we would have to deal with some specification

if we wanted to put constraints or limits on the size of the study involved.

DR. TOSTESON: It seems to me the issue of discretion is central. What I have in mind is that consider a situation in which the results at an interim point of a clinical trial raise the question of whether it is appropriate for the control subjects to continue to participate.

On the one side, one could argue that the person to make that decision is the control subject properly involved. And the point was made, both by Professor Casebeer and Professor Halpern, that we may not wish to be so proscribed; that that process of informed consent is not something that stops. There is always an obligation to consider whether it should go forward.

On the other side, there is the responsibility of the investigators, supported by the National Institutes of Health, to carry through the study in such a way as to get the most reliable data and then the question is, who is to decide.

DR. FREDRICKSON: There are discretionary issues that inevitably arise in this kind of arrangement. And it relates, I suppose, to this legal/ethical question of "continuing informed consent," which appears in one or two of the briefs that we have before us. There can be no question of the primacy of the interests of the subjects who are participating. And one must be sure to build into the data monitoring systems that we now have, and into the process of informed consent, sufficient means to represent the interests of the patients. I don't think that we are seeking to try to interfere with that

discretionary judgment in what we're trying to do. But I realize that it can be an issue.

DR. TOSTESON: It seems to me that places a heavy burden upon the NIH to frame the proposed exemption in a very clear way, so that this Board and others can have an understanding of the implications.

DR. FREDRICKSON: Yes, I think that's correct. We would have to accept that challenge.

CHAIRMAN GAITHER: I think we have to break. I think it would be helpful, particularly for those lay persons on this Board, to have some sense in whatever way you can get it before us of what is involved, without jeopardizing the principle that you are fighting for.

I would hope there would be a way, hypothetically perhaps, to give us the sense of the kinds of clinical trials that have either been conducted, or proposed or that are being conducted, and the kinds of jeopardy that we are trying to protect against here.

I think, certainly, a lot of us -- and I think our witnesses this morning -- are dealing with an abstraction that is hard -- at least for us lay lawyers -- to understand. And we very much appreciate your giving some thought to how we can come to grips with precisely what would and would not be involved here.

Unfortunately, we are behind schedule. Let us break now for lunch. For the audience, let me warn you that I think it will be difficult for us to be back by 1:30. I would assume it will be 2:00 before we resume.

組換えDNAをめぐる冒険旅行

RECOMBINANT ODYSSEY - TOKYO LEG, 1979

September 22, 1979

Last night, Dr. Kanamori flipped into my lap a copy of David Dickson's report in Nature of the most recent actions of the RAC, including the notation that I was likely to approve, with little alteration, the recommendation to eliminate most E. coli K-12 experiments from coverage under the Guidelines. We were, at the time, deeply engaged in EN-KAI, the unique Japanese system for getting down to serious business. The geisha at my side re-filled the cup with warm saki, poured from a little crock; my chop-sticks were sliding tentatively off the edges of a piece of raw fish, marinating in sauce; our shoeless feet were somewhere beyond our folded knees, which were tucked under the table, in the six inches of space between it and the floor. Soon the oldest geisha will begin to strum her 3-stringed samisen and we will clear away the inhibitions with a dance to the "Miner's Song," rhythmically shoveling imaginary coal and pushing invisible loads around the table.

Kanamori (Jinsaku Kanamori, M.D., Science Counsellor of the Planning Bureau in the Science and Technology Agency (STA); adr. 2-2-1, Kasuruiqaseki/Chiyoda-Ku, Tokyo) has been the activist at our counterpart talks held these last few days in Tokyo (September 19-21) on the "non-energy initiatives" of the

Carter-Fukada agreements to increase science cooperation between the U.S. and Japan. One of the six health-panel initiatives carried to Japan and accepted in advance by the Japanese for discussion has been Recombinant DNA Research. Our proposal, generated at NIH, has been designed with two objectives. The first is to open up clear channels between the U.S. and Japan that will allow us to understand the scope of DNA research in Japan and the source, structure, and changes in guidelines or regulation of such research in that country. The second--the purpose of this particular mission--is to urge the Japanese to augment their financial contribution to the basic research using recombinant technology, an area so far largely supported by the U.S. Particularly, we propose to the Japanese: (1) liaison between our respective RAC's or Japanese equivalents such that we will maintain comparable guidelines; (2) Japanese cooperation in, and fiscal support for, risk assessment experiments generally needed; and (3) an overall increase in Japanese spending in basic research, including host/vector development and other features of biological containment.

The general Japanese response in these negotiations--on most topics--has been one of enthusiasm by the technical experts and great hesitation to make any fiscal commitments--for the elections next fortnight in Japan include the discussion of a 40% deficit budget and increased taxation to cover it. A stony silence from the never-visible, never-absent Ministry of Finance has greeted the present U.S. overtures. In the recombinant area

we have received strong (informal) signs of desire to increase cooperation. The U.S. draft of the results of the counterpart talks contained the words: "The Japanese indicate willingness to increase liaison . . . on guidelines and risk assessment . . ." The Japanese replaced "indicate willingness" with "intend," and nodded frequently and affirmatively when I presented arguments for maintaining the universality of science, international parity in exploiting intellectual, social, and economic opportunities from these techniques, as well as noting that we ultimately share any ecological or other risks resulting from their use. The Japanese are interested in keeping pace.

They currently have about 70 projects in the country. There are about three P3 laboratories that are, as one of their experts put it, "real P3." Most experiments are P1 - P2. (P1 is not quite identical to ours, viz., they permit mouth pipetting.) They are planning to build one P4 laboratory for recombinant work and other high-containment research. Apparently Japan has none now. The impression was given us that Japanese industry is just getting started, and an image of Japanese engaged in many commercial projects, stewing vast volumes of E. coli K-12 or yeasts containing alien genes, is not a correct one at the moment.

At our Japanese "meeting" last night, our major host was Dr. Fujio Ohtani (or Ōtani), Counsellor for Science and Technology of the Ministry of Health and Welfare (MOHW). Kanamori is a protege of Ohtani's, and the latter is also patron of our

other host, Dr. Katsumi Meguro, a psychiatrist and Director of the Mental Health Division of the Ministry.* Meguro and I were co-chairmen of the Health Counterpart talks. All three, Meguro, Ohtani, and Kanamori, understand English fairly well; Meguro speaks it reasonably well. This delightful EN-KAI was not devoted to recombinant DNA, but more to acquainting Dr. John Bryant and myself with the sincere desire on the part of the MoHW and the STA to cooperate scientifically with the U.S., with the impossibility of promises without firm financial commitments, and also perhaps to help us appreciate Dr. Ohtani's important role in the scientific activities of MoHW. Ohtani, a "Westerner" (from Kyoto, as contrasted with the "Easterners" from Tokyo) is an M.D., born in 1924; he has been in the Ministry for 20 years and is the author of several books, copies of which were presented to us.

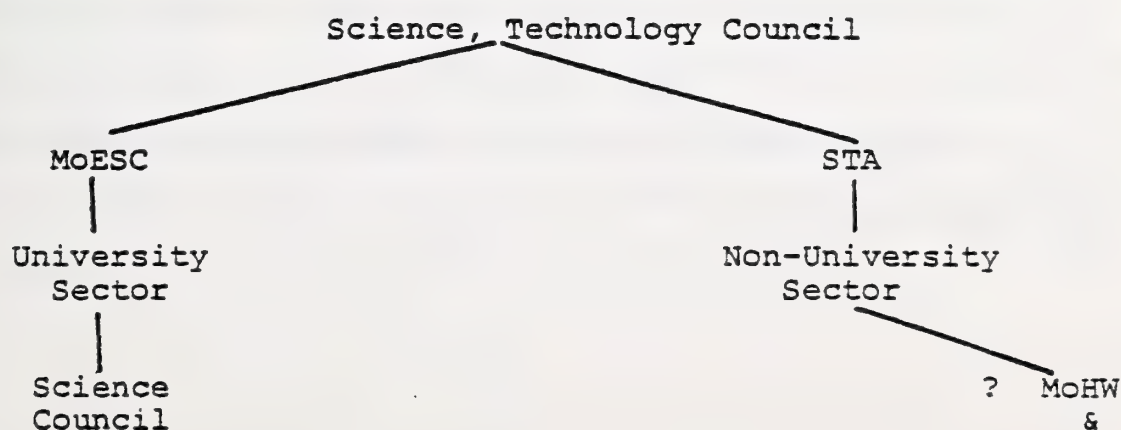
Most of the laboratory research on DNA is carried out in the laboratories and institutes supported by the Ministry of Education, Science and Culture (MoESC). Last month at the USJMRP meetings in Washington, Dick Krause and I met with Mr. Hitashi Osaki, Deputy Director-General, Science and International Affairs Bureau, MoESC. He indicated a desire to have close liaison with NIH in recombinant DNA affairs, and emphasized this by arranging a dinner for us at the Chinese Restaurant in the Okura Hotel,

* Also present were (1) Keiichi Nakabayashi, M.D., a psychiatrist and Director, Nishi Tokyo Hospital, Omo City 198, Tokyo, Japan; and (2) Miss Natsumi Sawada, Ministry of Foreign Affairs, tel. 580-3311, ext. 2395, Direct: 581-2924.

attended by some leading scientists and administrators in Japan concerned with DNA research. Attendees and seating arrangements for that are diagrammed in accompanying figures.

The non-industrial recombinant research in Japan is a concern of several ministries and other bodies, some of these having ministerial status. These include: the Japanese Science Council (once intended to be a "National Academy of Science" in Japan, current President is Kōji Huximi), the Science and Technology Council (at the level of the Prime Minister and probably the highest government-level source of advice), the MoESC, the STA (which has ministerial status), the MoHW, and the Ministry of Agriculture. The two Councils mentioned above must not be confused with the Science Council of MoE, for example. The latter is made up of university scientists and appears to function as an advisory body for the scientific activities of this ministry only.

The Japanese currently have at least two sets of guidelines. Unless our ecumenical example in the U.S., much recommended by me in the counterpart talks, has some magical effect on the traditional wars between Japanese bureaucracies, they also are likely to have other sets of guidelines, from Agriculture, the Health Ministries, and perhaps even STA. The current guidelines derive from relationships shown on the following chart:



The STC has issued guidelines, quite similar to ours. These (by virtue of the Prime Ministerial nature of the STC) are effective on all laboratories in Japan. The MoESC, through its Science Council, acts as an interpreter (apparently like a large I.R.B. or mini GMAG) of the guidelines as they are used in the laboratories supported by the ministry--the site of most of the grant-supported biological studies in Japan. The STA does the same for the non-university sector. It is not clear how institutional review or registration is maintained within institutions, or what is the extent of decision-making at each of the several levels or foci of control.

Dr. Kanamori and other Japanese presented us with copies of several sets of guidelines or documents. Some of these, I believe, we have earlier received at NIH, and included:

- (1) Response to Advice #8 "On the Fundamentals of the Policy for Promoting Recombinant DNA Research," dated August 9, 1979, published by the Science and Technology Agency (in Japanese);
- (2) Guidelines for Recombinant DNA Experiments (in Japanese), dated August 27, 1979---issued by the Prime Minister (no doubt through the Science and Technology Council); and (3) an English Translation: "Guidelines for Recombinant DNA Experiments in Research Institutions such as Universities, issued by the MoESC on March 31, 1979. These, according to our hosts, are based on our 1978 guidelines, although we need to ascertain the degree of correspondence.

The Japanese are au courant with the U.S. scene, as witnessed by the presentation to me by Dr. Kanamori of the piece from Nature, and also our receipt of Japanese translations of the NIH Guidelines, dated December 1978, and of the Federal Register insertion of April 11, 1979. During our counterpart talks there were other indications of how closely they are following changes in the guidelines. They insist their versions closely follow ours, but are stricter. They also are confident they cover all such work in Japan, because they bear the STC imprimatur, which envelops any edict with the power of the Prime Minister.

Our impressions of the overall bureaucratic complications possible in Japan--impressions heightened eagerly by our hosts--indicate that alterations in regulations or "guidelines" could take years. Given a healthy respect for industrial prerogatives in Japan, however, one would suspect that if the regulatory thicket became too dense, industry or individual ministries might find ways out on their own. We've no bases for predicting Japanese practices in the future, but it is evident that they are willing now to share knowledge of their rules and activities with us and will follow our movements with great interest.

At a reception given my Mr. Kaneko, Minister of State and Director General of the Science and Technology Agency, preceding our DNA supper on September 20, we met numerous Japanese scientists and aficionados of science and its bureaucracies. For example, Mr. Ikuda, the founder of SONY, was there, explaining his ideas

and new electronic inventions for teaching the Japanese language to youngsters in their first two years. Many septa- and octogenarian scientists were there, survivors of multiple passages through positions in universities, institutes, and bureaus or agencies. One, a nuclear physicist, and another, a former Professor of Biology at Tokyo University, were fascinated by the modern-day dilemmas of science as represented by the DNA controversy. The physicist, his chin whiskers wagging, suggested that NIH was "a most interesting invention" and that Japan "should have thought of this," as a relief from the paralyzing conflicts that often arise between separate ministries, universities, and government laboratories. In countries where universities are nearly all financed by the government, fragmentation of the support for health science between separate Ministries of Education/Health/Science, etc., can be quite destructive. Here lies an important lesson for the U.S. as it embarks on the fission of HEW.

Despite all the "gaps" between the administrations above them, the scientists manage, as usual, to keep in effective communication. Drs. Iino and Watanabe will be at NIH in November to foster liaison on guidelines, risk assessment, and research on DNA, in general. They can also enlighten us further on the complicated structures and lines of authority we have glimpsed, but don't fully understand. Professor Watanabe is chairman of the Recombinant DNA Committee of the Science Council, MoESC, and Professor Iino is chairman of its safety subcommittee.

Because there are advantages in, and even a stark necessity for, cooperating--if two such advanced countries are to get their share of profit from recombinant DNA activities--this field of research could be an important opportunity for Japan and the United States to experiment in novel interagency coordination. I have, at least, suggested this strongly to the numerous delegates and staff members at the counterpart talks. Who knows? Perhaps the stock of Yankee inventions--described in Japanese editorials as being sadly depleted--contains yet one exportable technology still unknown to the East. Wait until the "interagency coordinating committee" (brought to flower in NIH) catches root in the land of bansai!

Donald S. Fredrickson, M.D.

- Dr. Donald Fredrickson, Director, National Institutes of Health
- Dr. John H. Bryant, Deputy Assistant Secretary of International Health, Department of Health, Education and Welfare
- Dr. Rudolph Marcus, Scientific Director, Office of Naval Research
- Mr. Hitashi Osaki, Deputy Director-General, Science and International Affairs Bureau, Ministry of Education, Science and Culture
- Mr. Itaru Watanabe, Professor, Faculty of Medicine, Keio University (Chairman, The Recombinant DNA Committee, Science Council)
- Dr. Tetsuo Iino, Professor, Faculty of Science, Tokyo University (Chair, Recombinant DNA Safety Precaution Subcommittee)
- Dr. Wataru Mori, Adviser for Higher Education; Professor, Faculty of Medicine, Tokyo University.
- Mr. Motohiro Shitchida, Director, Science Division, Science and International Affairs Bureau, Ministry of Education, Science and Culture.
- Mr. Takashi Okado, Director, Research Aid Division, Science and International Affairs Bureau, Ministry of Education, Science and Culture.

Attended dinner in Chinese Restaurant, Okura Hotel, on September 21, 1971 (TO-KA-LIN)

FOR RELEASE UPON DELIVERY

STATEMENT BY
DONALD S. FREDRICKSON, M.D.
DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON
NUTRITION RESEARCH

BEFORE
THE SUBCOMMITTEE ON NUTRITION
COMMITTEE ON AGRICULTURE, NUTRITION, AND FORESTRY

UNITED STATES SENATE

October 2, 1979

National Institutes of Health
9000 Rockville Pike
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Accompanied by: Artemis P. Simopoulos, M.D.
Chairman, NIH Nutrition Coordinating Committee

Mr. Chairman and Members of the Subcommittee:

Thank you very much for this opportunity to appear before you once again to discuss the expanding program in nutrition research and research training at the National Institutes of Health.

Nutrition presents us with some challenging opportunities in basic biomedical, clinical, behavioral and social science research. Biomedical research is aimed at understanding the complex physiological processes that occur in living things. These include the molecular interactions and enzyme catalyzed reactions within cells involved in metabolism and the utilization of energy by the cells. Clinical research examines the role of diet and nutrients in both the healthy and the diseased state of human beings. It seeks to translate to man what is learned in all forms of life concerning the role of diet and the nutrition process. In behavioral and social science research we seek the decision-making factors which determine life style, food preferences, and ultimate health status of individuals and groups of individuals. Nutrition research works at constructing a broad mosaic of valuable contributions from many disciplines and specialties.

I would like briefly to tell you about five major areas in which the NIH nutrition program has expanded since the time of the hearings last June:

- Clinical Nutrition Research Units;

- Investigator-initiated research;

- Nutrition research training;

- Nutrition education; and

- Coordination of efforts among Federal agencies.

Clinical Nutrition Research Units

The NIH has considered expansion of its clinical nutrition research program for some time and determined that a most appropriate mechanism for such expansion would be the development of Clinical Nutrition Research Units throughout the United States. Most of these units are to be associated with medical schools, schools of public health, and research hospitals, although they are not limited to these settings. The NIH will fund four such Clinical Nutrition Research Units in FY 1979, and we hope to fund more in FY 1980. The four Clinical Nutrition Research Units funded in FY 1979 and their principal investigators are the following: Alfred E. Harper, University of Wisconsin; Harry L. Greene, Vanderbilt University in Nashville; Irwin H. Rosenberg, University of Chicago; and C.E. Butterworth, Jr., University of Alabama.

A Clinical Nutrition Research Unit, or CNRU, is an integrated array of research, educational, and service activities oriented toward the study of human nutrition in health and disease. A primary component of these units is training. The program is designed to strengthen the environment for improved education of medical students, house staff, practicing physicians, and paramedical personnel in clinical nutrition. Stimulation of research and training will, in turn, enhance nutritional care of patients and promote the generation of more useful nutritional information for the public.

The NIH has previously sponsored component activities of CNRU's through a variety of more traditional awards--principally research project grants and support for research training. The present initiative to

provide core grants for shared facilities and multidisciplinary interactions with medical schools, universities and hospitals is an important addition. This approach also tends to ensure that activities of CNRU's have broad sponsorship and reduces the likelihood that they will become unduly dependent upon any one source of funds. Our own Clinical Center in Bethesda has many component activities of a Clinical Nutrition Research Unit. We seek to integrate them while respecting their location within the intramural research program of the several institutes. The new Ambulatory Care Research Facility (ACRF) will certainly facilitate expanded studies in intramural ambulatory populations. We lack a medical student body, but we have other advantages--for example, the lay public in the surrounding area and many special patient populations in which we are already conducting experiments with better nutritional instruction.

Investigator-Initiated Research

Most of the nutrition research supported by the NIH is initiated by investigators outside the agency. For example, in FY 1978 the NIH funded 861 research project grants in nutrition for a total of nearly \$52 million. Agency-initiated research, through 137 contracts and 64 centers, was \$29.7 million.

Because we believe that the most creative research is that which is investigator-initiated, we have taken steps to stimulate efforts in this area by issuing a number of Program Announcements (PA's) and Requests for Applications (RFA's). Some of the topics where we have sought increased attention are: infant nutrition; nutrition in relation to health of the aged and the aging processes; nutritional aspects of

cancer etiology, prevention, treatment and rehabilitation, and studies on overnutrition and obesity.

In addition to the development and issuance of RFA's and Program Announcements designed to enhance our nutrition research program, we have held eight nutrition conferences to review the state-of-the-art, to stimulate research in selected basic areas, and to identify those developments in research that can now be applied.

The NIH is also expanding its program in nutrition research through the contract mechanism by issuing numerous Requests for Proposals (RFP's) in a variety of areas of nutrition research.

Both the National Institute of Child Health and Human Development (NICHD) and the National Institute on Aging (NIA) have expanded their programs in clinical nutrition. The NICHD has created a new program in clinical nutrition and early development to stimulate research on how behavioral, cultural, and social factors affect diet and nutrition. This program has funded research to do the following:

- Document the prevalence of food sensitivities or idiosyncratic food metabolism in various populations;
- Carry out studies designed to determine the genetic, biochemical and physiological mechanisms that cause food sensitivities or idiosyncratic reactions to foods; and
- Determine whether dietary patterns early in life are conducive to food sensitivity and idiosyncratic food metabolism.

The NIA is implementing an extensive program in adult clinical nutrition. With this program, the NIA is beginning to build the first comprehensive

body of new knowledge on dietary intake, nutrient utilization, and nutritional status of the aged, and to provide better understanding of how these factors help maintain optimal health in this population.

As you know, in 1978, appropriations for Agriculture, Rural Development, and Related Agencies programs included the establishment and funding for two nutrition research centers--a Children's Nutrition Laboratory at Baylor College of Medicine, and the Human Nutrition Research Center at Tufts University, to study diet and nutritional status in the aging process. Memoranda of Agreement have recently been signed between USDA and the NIH ensuring close cooperation of NICHD and NIA in planning and implementing the programs of these new centers.

Research Training

The success of any research program depends upon a continuing supply of bright, young scientists. Clinical nutrition research has not been the destination of enough of the top aspirants in the past two decades. There are signs of a renaissance, however. In order to encourage the most promising students to pursue research training in nutrition, the Nutrition Coordinating Committee, with the strong support of many of the Institutes of NIH, has issued two Program Announcements within the National Research Service Award program. One is designed to provide postdoctoral research training to individuals to broaden their scientific backgrounds and convert their efforts to research in nutrition. The other is designed to enable institutions to make training grants to individuals selected by them for predoctoral and postdoctoral research training in nutrition. Currently, the NIH is supporting 200 individuals

in the area of nutrition research training. This figure includes 169 training grants and fellowships as well as 31 NIH intramural trainees. In addition, the NIH supports 37 Research Career Development Awards (RCDA's) and 11 new, young, and academic investigator awards, for a total of \$3.9 million.

Nutrition Education

The NIH Nutrition Coordinating Committee established a permanent Subcommittee on Nutrition Education in October 1978. This multi-disciplinary subcommittee includes dietitians, physicians, communications experts, and educators among its membership.

The charge of the subcommittee is to review NIH nutrition documents designed for the public prior to their publication; to develop public service announcements for radio and TV; to develop films on nutrition; and to develop an NIH Newsletter on Biomedical and Behavioral Research and Research Training.

The Nutrition Coordinating Committee, through its Subcommittee on Nutrition Education, hopes to begin publication of a Nutrition Newsletter in 1980. This bimonthly publication would be generally intended for nutrition professionals, including NIH grantees, members of the National Nutrition Consortium, Federal agencies, state health departments, medical schools, schools of public health and schools of nutrition, private foundations, committees of Congress and their staff concerned with nutrition, the Office of Technology Assessment, and the concerned public. It will include regular features of interest to the nutrition community.

As I mentioned earlier, this September, the DHEW Nutrition Coordinating Committee held a two-day national conference on "Nutrition Education in the 1980's." Over 50 percent of the financial support for the conference was provided by the NIH, and the conference was held on the NIH campus in Bethesda. In addition, the recently published Surgeon General's Report on Health Promotion and Disease Prevention, Healthy People, identified nutrition as one of 15 distinct disease prevention/health promotion areas. The NIH program on nutrition has contributed substantially both to the Department's programs on nutrition and prevention, as well as the Surgeon General's Report.

Coordination of Nutrition Programs Among Federal Agencies

As I'm sure you're aware, the Office of Science and Technology Policy, in the Executive Office of the President, has established a Joint Subcommittee on Human Nutrition Research. This Subcommittee is composed of representatives from DHEW, the Department of Agriculture, the Department of Commerce, the National Science Foundation, the Department of Defense, the Department of State, the Federal Trade Commission, and the Veterans Administration. It is co-chaired by Dr. Mark Hegsted of the Department of Agriculture, and Dr. Artemis P. Simopoulos, of DHEW/NIH. The office of the NIH Nutrition Coordinating Committee is responsible for the Executive Secretariat functions of the Subcommittee.

The purpose of the Subcommittee on Human Nutrition Research is to increase the overall effectiveness and productivity of Federal research efforts in nutrition. In fulfilling this purpose, the Subcommittee will: improve planning, coordination, and communication among Federal

agencies engaged in research and training in nutrition; develop and update plans for Federal research programs to meet current and future domestic and international needs for nutrition; collect, compile, and disseminate information on nutrition research; and prepare reports describing activities, findings, and recommendations of the Subcommittee.

We believe that the NIH has indeed continued to sharpen its nutrition research training program and to expand it. Each one of the five areas I have described--Clinical Nutrition Research Units, investigator-initiated research, nutrition research training, nutrition education, and comprehensive coordinating efforts among Federal agencies--plays a vital role in the overall success of this important research effort.

I shall now be happy to answer any questions from the Subcommittee members and staff.

MEMORIAL CEREMONY FOR DR. ARNOLD WEDUM ^{1/}

Remarks by Donald S. Fredrickson, M.D.
Director, National Institutes of Health

We are here to honor Dr. Arnold Gerhard Wedum who has contributed so much to microbiological safety and whose work has enabled scientists to conduct studies of infectious diseases that would not otherwise be possible.

The Army has already recognized Dr. Wedum's contributions to its programs. In October 1959, he was awarded the Army's Exceptional Civilian Service Decoration for his work in Microbiological Safety. In 1969, Dr. Wedum was awarded the Department of the Army Certificate of Achievement, and in November 1972, he received the Department of the Army Decoration for Meritorious Civilian Service. The safety program directed by Dr. Wedum at Fort Detrick was so successful that the National Safety Council presented its highest award - the Award of Honor - on five different occasions.

I am privileged today to represent the NIH and the biomedical research community as we honor Dr. Wedum for his extraordinary contributions to microbiological safety and to the progress of biomedical research. As a physician, he recognized the essential need to develop and use safe techniques to control occupational risks associated with the study of infectious microorganisms. As a scientist, (Ph.D. in microbiology

^{1/} Presented at NCI Frederick Cancer Research Center,
October 16, 1979

he knew that the integrity of experimental results was dependent on effective and practical containment techniques and safe practices. He realized that progress in infectious disease research would be constrained unless the health and safety of those participating in this work could be protected and the community and environment not be placed at risk.

As a leader, he gave of himself unselfishly to nurture scientists, managers and safety professionals alike in the art and science of microbiological safety for he knew that safety was ultimately the consequence of the action of people.

Dr. Wedum pioneered studies to assess the risk to workers engaged in infectious disease research and with the insights he gained, organized programs to develop techniques and equipment to minimize these occupational hazards. These programs have influenced the development of most microbiological safety equipment in common use today. The universally used Class I biological safety cabinet was developed by Dr. Wedum and his colleagues (many of whom are present today). Also developed under his direction was the Class III gas-tight cabinet system that allows research to be carried out safely with even the most exotic and dangerous types of pathogens.

Dr. Wedum published more than 80 articles in scientific journals and contributed chapters to several books. His critical reviews in risk assessment have provided the foundation for estimating the risk of human infection during research in

the microbiological laboratory. This important contribution has enabled the laboratory scientist to select appropriate safeguards. The training films he produced with the U.S. Public Health Service continue to be used to this day to teach safe microbiological laboratory techniques to scientists, students, and technicians.

The development of biological safety principles under Dr. Wedum, including laboratory design, safety devices, the behavior of biological aerosols, the pathogenesis of respiratory infection and the medical management, prophylaxis, immunization, and therapy of such diseases, has enabled military and civilian biomedical research laboratories to undertake studies on highly infectious microorganisms with comparative safety.

One of the most far-reaching of Dr. Wedum's many contributions has been his leadership in formulating criteria and regulations for the shipment of etiologic agents and biological materials. He realized that cooperative arrangements, safeguards, and appropriate controls were needed to assure that etiologic agents could be transported in a safe manner but without undue restrictions. Through the years Dr. Wedum spearheaded this effort for the Department of Defense. He worked with officials of the U. S. Public Health Service in development of regulations on the shipment of etiologic agents, and more recently with the Department of Transportation when that agency took over primary responsibility for the shipment

of hazardous materials. The success of Dr. Wedum's work in establishing safe methods for transporting etiologic agents is demonstrated by the fact that there has never been an infection associated with the commercial or military transportation of biological materials under Army sponsorship. The present Federal codes and regulations governing the transportation of etiologic agents are in large part derived from the methods of packaging, testing and shipping of these materials that were developed and established at Fort Detrick under Dr. Wedum.

Dr. Wedum made invaluable contributions to the NIH in the area of microbiological safety. He was the principal advisor to the NCI during the formative stages of its biological safety programs. He was always available to give guidance to the evolving safety program of the NIH as well as to the individual scientists who sought his expertise. He encouraged NIH to provide National leadership in microbiological safety and because of his steadfast work, we are the beneficiaries of his legacy.

I am particularly grateful for the exceptional guidance he provided to the NIH in the development of the physical containment measures for recombinant DNA research. His technical contributions and safety philosophy are embodied in the fabric of the current NIH Guidelines for Recombinant DNA Research.

Up to this point it will not have escaped you that I have been describing the contributions of an exceptional man, but one I did not know personally.

I have seen him reflected, however, in colleagues who were strongly influenced by him . . . safety experts such as (Manny) Barbeito, (Everett) Hanel, and--especially--Emmett Barkley.

In their dedication to an ideal of safety and reduction of hazard to permit realization of the promise of science, one sees the preceptor, Wedum. One sees not only his reasonableness and wisdom, one also sees his unselfish pleasure at helping others realize the potential of themselves and their arts.

Above all, one senses the infectious enthusiasm of Arnold Wedum. Pasteur, whom Wedum seems to resemble a little in retrospect, has something to say about quality. "Enthusiasm," Pasteur said, "is one of the most beautiful words given us by the Greeks. It comes from EN THEOS--a god within."

Today we pay respects to a person of enthusiasm, in that best sense the Greeks intended.

It is an important gift. Those who have it live among us well beyond their natural lives. For this reason we meet today to commensurate the influence and contributions of Arnold Wedum.

I'd like now to introduce Dr. Arthur C. Upton, Director of the National Cancer Institute, who will tell you briefly of Dr. Wedum's special contributions to the National Cancer Program.

#

DEDICATION

It is my privilege and honor to dedicate this plaque in memory of the Father of Microbiological Safety, Dr. Arnold Gerhard Wedum.

THE MEANING OF THE PRIZE*

The First Lita Annenberg Hazen Award for
Excellence in Clinical Research
Presented to Dr. Jesse Roth

DONALD S. FREDRICKSON

A number of years ago I attended the gala presentation of a scientific award in the Midwest. The scheduled orator after dinner was the vice-president. However, he defaulted at the eleventh hour and I was pressed into service as his replacement. I rose to state the meaning of the prize. Unballasted by preparation, I had us quickly at heights rivaling the recent flight of the balloon Da Vinci. Eventually I was depicting mankind walking blindly about in a vast, darkened cave, and soon was groping for a Wagnerian climax to rescue both civilization and a badly overextended oration. It came to me in a flash. I described how rare heroes would occasionally hurl firebrands aloft. The torches would stick high up on the sides of our gloomy cave, and briefly, but brilliantly, we could see where we were and where we had to go. "Only a few can have the prize," I concluded dramatically, "but we can all share the light." At my side, our host calmly brushed off the ashes of the burning metaphors and leaned over to me. "At least," he said, *sotto voce*, "we can all share the dinner."

I promise no flame-throwing tonight. Just a cozy chat with our hostess, if she doesn't mind. The rest of you may eavesdrop if you wish. The occasion is much more than a dinner, Mrs. Hazen, although we are all grateful to be the guests of your hospitality.

The giving and the receiving of this first Lita Annenberg Hazen Award for Excellence in Clinical Research has special meanings for some and general meanings for all of us.

The Special Meaning

Ramón y Cajal was a famous histologist, the

**Remarks on the occasion of the presentation of the first Lita Annenberg Hazen Award for Excellence in Clinical Research to Dr. Jesse Roth, at the St. Regis-Sheraton Hotel, New York, New York, November 1, 1979.*

Requests for reprints should be addressed to Dr. Donald S. Fredrickson, Director, National Institutes of Health, U.S. Department of Health, Education, and Welfare, Bethesda, Maryland 20014.

first scientist in Spain to win a Nobel Prize. In a wonderful little book, he counseled us about science and being a scientist. "The psychology of the investigator," he said, "...includes two emotions which act with unusual vigor: his devotion to truth and a passion for reputation."¹

Here you have the fundamental equation behind much of the energy and dedication of scientists. It is the source of a vital tension. Truth must be kept above reputation. There is no lasting reputation without truth; and often truth is the only reward. The act of adding a little truth to the world's precious supply is itself the source of an enormous "high." No monetary prize is immediately comparable. To be judged "most valuable player," however, does add important reassurance to one's own estimate of worth. Again, the amount of added esteem is measured more in the quality of the jury and the strength of the competition than in the size of the prize. It is true, though, that the latter has much to do in determining the former.

Having paid our due to the moralities, we ought not to appear to deny the virtues of cash rewards. Dr. Jesse Roth—and I, too—like to think we work for mankind, but our particular paymaster is the federal government. Annually, Congress confuses the HEW appropriation with abortion legislation, and the pump gurgles dry for a month or so. As the fiscal year began again this October, only Jesse Roth among the 12,000 employees at the National Institutes of Health knew *he'd* be paid at the end of the month!

Ramón y Cajal did not neglect in his memoirs to give instructions on how a scientist should choose a wife. As part of that, he muses about the sharing of fame or the prize if it comes. "The modest wife deserves it also, for thanks to her self-denials... she made possible in the end the execution of the great undertaking."¹ I must leave it to Susan Roth, and perhaps to Elisa, six, and Alexander, five, to speak for themselves about this. They must also speak for Alana, whose first six months have probably not given

her time to get familiar with her father's laboratory.

Whether the tangible rewards to the family become a mountain of fried chicken, a new woodcut, or finally getting the house on Linden Street painted, it is their private affair. I can only say for them how well I know that wives and families are sometimes heavy losers when a scientist chooses the search over personal income. A prize can be welcome compensation for sacrifices not always anticipated during courtship.

Like the rings excited by a stone thrown into a pool, there are widening circles of persons beyond the winner who also are affected by an award. No one wins a prize like this all by himself. Maurice Strauss likened scientific advances to the "living layers of a coral reef built on the past labors of countless predecessors."² A good analogy, but a trifle impersonal.

In reviewing his own work, Jesse Roth, tonight's prize-winner, has expressed his indebtedness to: Gordon Tomkins,³ a pioneering, yet contemporary spirit who had an infectious faith that abstractions called receptors sat outside cells and converted the touch of familiar passers-by into messages of importance to the community of molecules within; to Berson and Yalow, preceptors who crafted the basic methods to prove the theories correct; and to the many colleagues with whom Dr. Roth adapted the methods for testing each new hypothesis, dissected the failures, and endlessly changed and pursued the new experiments, and with whom he shared the exultation as the circle closed and the skeptics yielded.

Each individual whose life has had contact with the subject of a recognized discovery is apt to feel some change in his sense of worth. Usually self-esteem goes up; but there are resonances in a minor key that can be excited by the giving of a major prize. A scientist usually rises at some expense to the reputations of other scientists who helped create his special opportunities. The fixing of truth to a new level invariably wrenches at the previous settings. Both Newton and Harvey discredited some of the work of Descartes. Many of the early astronomers refuted the interpretations of their predecessors. On the way up, Watson and Crick jostled Rosalind Franklin, and put down Linus Pauling, too.⁴ There is no

master who, at some time, has not been bumped by his apprentice. We can sometimes understand the nobility of our art—and appreciate the mortal side of scientists—in the manners of those who have narrowly missed the prize.

A prize also brings pleasure to the institution of the awardee. This first presentation of your prize, Mrs. Hazen, brings double joy to the National Institutes of Health. The Hazen Award is unusual in providing an equal sum to the institution so that research fellows may be supported in the laboratory of the winner. It is a generous and a prudent provision for the continuity of the work that has been recognized, and also, a clear statement of one purpose of the prize: to honor scientists who are in a fully productive phase of their careers.

Dr. Roth conducts his research in the intramural program of the National Institute of Arthritis, Metabolism, and Digestive Diseases. The clinical research of this Institute, like that of most of NIH, is carried out in the Clinical Center in Bethesda, Maryland. I can attest to the pleasure these overlapping institutions enjoy in vicariously sharing the first of these awards.

For the past 25 years, the Clinical Center's output of skilled scientist-clinicians has been unrivaled. Consequently, we felt it was highly probable that the Hazen award would go to at least an alumnus. But for the first to be made to an incumbent scientist is, to us, a most gratifying confirmation of the Center's current contribution to clinical research.

The Clinical Center was erected at NIH by a unanimous Act of Congress in the early 1950s.⁵ With its 500 beds amidst a thousand laboratories, it became a giant version of its progenitor, the proud and still productive Rockefeller Hospital, which had opened just 40 years before. The two institutions, along with the establishment of the first clinical unit system at Johns Hopkins in 1913, mark time-points in the rise of clinical research in 20th century America to a level unparalleled in history. Lately, we have undertaken modernization of the Clinical Center to expand research on ambulatory patients. Walking recently among the scaffolds, I thought proudly of including the receipt of the Hazen Award by Jesse Roth with the objects to be sealed in a renewal of the cornerstone. . . . (Just the *receipt*, Jesse, not the prize!)

The Elusive Definition

With establishment of this award, fuel has been added to a long-smoldering debate as to just what is meant by the term "clinical research." At the initial meeting of the selection committee, I understand the definition remained elusive. Because I was not there, I will add here my own opinions.

There is a strong sentiment that clinical science was the child of William Harvey, whose treatise *De Motu Cordis*, in 1628, was the first description of the circulation of the blood.⁶ Harvey's epistemology stood on three legs: learn from the living man, learn from the dead man, and learn from the living animal.⁶ Harvey's followers had trouble maintaining so broad a stance. After his death, physiology budded from medicine, and biochemistry budded from physiology, while clinical science withered.^{6,7} The great clinicians, from Sydenham (1624-1689), who was Harvey's contemporary, to Osler, the "Canadian-American Hippocrates" (1849-1919), preferred perfect description to careful experimentation.

For my taste, the first modern clinical scientist was not even a physician, but a chemist. He cured sheep, beer, and silkworms of their diseases before he was ready to perform a daring clinical experiment on two boys bitten by rabid dogs. To think of Louis Pasteur is to remember that it has only been about 100 years since people stopped believing that living things arise spontaneously. It's also just as recently that people were convinced that bacteria cause disease. It gives us further pause to remember that Pasteur's genre will not be found in the clinic today. But the requirement for medical or nursing qualification, if one is to be at the bedside end of clinical science, is no cause to be wistful for an unregulated past. A century's growth in caution about participation of human subjects in research has been good for them and for science as well.

René Dubos reminds us that Pasteur had no hang-ups about distinctions between basic and applied science.⁸ "There is only science and the application of science," he said. The 19th century ideal represented by Pasteur, or by the physician Robert Koch, leaves us in awe of both their opportunity—and their ability—to create whole disciplines. Both were model scientists, rare at

any time in history in their skills at observation and experimentation; both were indefatigable laboratory workers who had no image-problem about "going practical" when need coincided with a good opportunity.

In the 20th century, the dazzling specialization required by modern scientific techniques has often strained the definition of clinical research. The ideal has moved back and forth like a pendulum between Pasteur's holistic example and fastidious maintenance of the "Cartesian dualism"—separate realms for science and for man.

In 1910, when the new Rockefeller Institute for Medical Research opened its doors, the pathologist Theobald Smith asked his fellow board members about their intention to appoint Jacques Loeb, the physiologist. "What is... the relation of these experiments with sea urchin eggs to medical research?" Smith demanded. The Institute took such ambivalence in stride in adopting a definition for medical research as that which "might contribute to understanding of health and disease... whether it involved the body of a suffering man or the study of subatomic particles."⁹

In intervening years, however, many notable scientists, from that same Jacques Loeb¹⁰ to Hans Krebs,¹¹ have warned biologists to beware of a narrow parochialism. I like Strauss' way of making the point, by pulling out Eddington's comments on entropy—that eminently useful concept of physics.⁷ To Eddington the idea of entropy—a measure of randomness—was the greatest contribution of the 19th century, because it shifted a preoccupation with the single parts of a system to a view of their action and nature as a whole.¹² Certainly for the clinical researcher, whose main subject is man, a serious metaphysical error would be to forget Dwight Ingle's aphorism "the whole system is the reality."¹³

In the early 1900s, Great Britain imported the clinical research unit from America.¹⁴ It gave the descendants of Harvey opportunity to deliver some still-remembered lines on the optimal fusion of scientist and physician in the new systems of medical research and training. What is required, said Allbutt in Cambridge, is one who has a "footing in both camps."¹⁵ Sir Charter Symonds made clear where he thought the right

foot was to be planted, by adding that "however well informed a man may be in the preliminary sciences, the final court of appeals is at the bedside."¹⁶

In 1933, Sir Thomas Lewis, the chief of clinical research at University College Hospital, rises before the Royal College of Physicians to give the annual Harveian Oration.⁵ Let us attend his remarks. At first, it is as though Harvey himself is speaking:

... a problem primarily concerning the living, in part concerning the dead, and in part deriving from the laboratory....

Then, the voice becomes Sir Thomas, the physician, speaking:

Knowledge that is applied usefully to the health of mankind will always come by a series of steps, the first of which is the recognition of the human needs, the last of which is the application of a test directly to the human problems....

We can imagine Harvey insisting here:

Yes, but between these "clinical" steps there must proceed all manner of search among the secrets of nature, with reference only to what is true and not to what is practical....

Sir Thomas, whose lecture it is, gets in the last word:

He who can see the source of the problem, who can appreciate the fittingness of its final solution, is uniquely fitted to guide the whole train of thought and inquiry....

What do we hear in this antiphony that we can use as the essential mark of the kind of science called clinical research? I hear one note above the others: an emphasis on the whole being; a sensitivity to the aggregate qualities and their organization that make each person different and man the most complex and interesting of all the living things.

I think that Jesse Roth—in his attention to the need of the diabetic patient for understanding of his threatening disability, his superb and sweeping view of a potential explanation, and the painstaking application of the test to many individuals—has passed the crucial test of sensitivity. He merits this prize, and our highest praise and congratulations.

I know from long, personal experience that the hybrid profession of clinical research is not the simplest calling. As a scientist, one finds the usual methods constrained because human

beings are the experimental subjects. As a physician, one finds it wrong to be restricted to disinterested observation. With one's patients, it is often necessary to convey a conviction in miracles while silently believing in the laws of probability.

Today, to many physicians, the demands of clinical research often seem too great when measured against the higher certainty of success, the less competitive pace, and the greater monetary rewards of the alternative pathways. The creation of this prize is a statement of encouragement to those who may hesitate to accept the challenge.

The Ultimate Meaning

I will end this homily close to where I began, by reference to another thought of Ramón y Cajal. In judging the important qualities of a scientist, he picked one that seems a little dated. One of the five attributes of a good scientist, he wrote, is patriotism.¹

As with the coral reef, countries and cultures layer their special contributions upon accretions from preceding civilizations. Each nation has its special times of glory; and while the sciences and the arts are inherently universal, they also come in national flavors. The history of medicine will record that this has been America's century—mainly because of the amount and the quality of its medical science in this era. This gentle form of supremacy is in turn, largely attributable to an American tradition of generosity toward support of research.

The Lita Annenberg Hazen Award for Excellence in Clinical Research has the scale and grace of that tradition. Although the Constitution is silent on government patronage of research, the growth of federal support of health research since World War II is a latter-day expression of the original spirit of the Founding Fathers. There are many signs now that science in America must endure a rising pessimism and general austerity. But the search for truth and reality must continue as one of the essential operations. This generous gift to stimulate clinical research is a gesture that will strengthen the compact between science and the citizen.

In the final analysis, Mrs. Hazen, this symbolic renewal of the social contract may be the most important meaning of your prize.

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HEALTH RESEARCH: FUTURE DIRECTIONS

HEARING
BEFORE THE
SUBCOMMITTEE ON
HEALTH AND THE ENVIRONMENT
OF THE
COMMITTEE ON
INTERSTATE AND FOREIGN COMMERCE
HOUSE OF REPRESENTATIVES
NINETY-SIXTH CONGRESS
FIRST SESSION
ON
POSSIBLE FUTURE DIRECTIONS AND POLICIES IN HEALTH
SCIENCES RESEARCH

NOVEMBER 14, 1979

Serial No. 96-75

Printed for the use of the
Committee on Interstate and Foreign Commerce



U.S. GOVERNMENT PRINTING OFFICE

55-483 O

WASHINGTON : 1980

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HEALTH RESEARCH: FUTURE DIRECTIONS

WEDNESDAY, NOVEMBER 14, 1979

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2123 of the Rayburn House Office Building, Hon. Mickey Leland presiding (Hon. Henry A. Waxman, chairman).

Mr. LELAND. The Subcommittee on Health and the Environment will commence.

Let me begin by reading Chairman Waxman's statement. Today's hearings will examine possible future directions and policies in health sciences research. It will focus primarily on the underemphasized research area of disease prevention and health promotion.

As the chairman of the Health and the Environment Subcommittee, I regard this first hearing on health sciences research as both timely and critically important. This hearing will offer us an opportunity to hear important viewpoints about possible future directions in health research before we move to consider upcoming legislation to reauthorize our biomedical research authorities.

As the total health care system faces significant opportunities and challenges in the upcoming decades, I view this subcommittee's legislative and oversight activities in health sciences research among our top priorities.

Health sciences research offers perhaps the greatest hope for discovering new ways to prevent disease, to reduce the enormous human suffering and economic losses from illness, and to improve the quality of life and health of the American people.

The potential benefits that could accrue from disease prevention and health promotion research are great. Consider high priority health areas such as cancer, heart disease, occupational health, accidents, obesity, infant mortality, smoking, alcohol, and drug abuse.

These are among our Nation's most serious health problems. Yet despite their seriousness, there are critical gaps in our knowledge—gaps that can only be remedied by a significant commitment to basic, applied, and epidemiologic research clearly oriented to disease prevention and health promotion.

I was particularly gratified to see the Surgeon General's recent report on health promotion and disease prevention. The report reflects a growing appreciation of the importance of disease prevention and health promotion research among policymakers in Washington, and the American people.

There are activities that the Department is at this particular time, through the National Institutes of Health and through other agencies, in fact, acting to strengthen, and they include building on some of the lessons we have learned in our community-based risk factor intervention trials that were described to you earlier.

They include the long-term, population-based epidemiologic studies that can help to identify risk factors not only of cardiovascular disease but for cancer, as well. They include efforts now being strengthened by the National Institute of Child Health and Human Development to identify the childhood determinants and antecedents of behavior that can be harmful to health.

They include efforts to evaluate health education and health promotion programs that are to be undertaken in key settings such as the school and work site. Again, we cannot predict the probability with a great measure of confidence at this point that these research efforts will be absolutely productive in terms of increasing our ability to prevent disease, but we feel these are the kinds of activities that can be most helpful in strengthening our understanding of measures to prevent disease.

Mr. GRAMM. Let me follow that up by asking what activities could this subcommittee undertake that would put emphasis on disease prevention and health promotion, given that we face a real financial constraint. This is increasingly binding.

How would you like to see us redirect funds we are spending toward promoting general health care?

Dr. MCGINNIS. I am not sure redirection of funds is necessary. I think at this stage, one of the most useful and important contributions the committee could make would be to work with your colleagues on the appropriation side to see that the proposals that are made in the President's budget in support of the activities that have been stimulated through previous legislation that you have had the foresight to develop and pass are indeed implemented.

One of our problems at this point is an inability to have those programs receive appropriations that you and we feel did warrant support.

Mr. GRAMM. Let me thank you, Dr. McGinnis, for appearing before the subcommittee. Your testimony, of course, will be in the record as we move into the area of authorizing legislation as it relates to preventive medicine. I think your input will be important, and I would like to thank you for coming.

Dr. MCGINNIS. Thank you.

Mr. GRAMM. I would like to next call Dr. Donald Fredrickson, Director of the National Institutes of Health.

STATEMENT OF DONALD FREDRICKSON, M.D.

Dr. FREDRICKSON. Thank you. It is a pleasure to appear before you this afternoon.

I think I will not read all of my opening statement but ask your permission to submit it for the record. [See p. 95.]

Mr. Gramm. I think that would be very helpful, given that we have legislation on the floor. Obviously, I am the only member here, so people are going to read your statement. So if you could summarize it and then we could just go with questions.

Dr. FREDRICKSON. Very well, Mr. Chairman.

Among those questions you may have about the National Institutes of Health or NIH this afternoon is the question of how does it set its priorities, and particularly the relationship of its activities to the question of prevention of disease and health promotion.

I think, Mr. Chairman, I would like to begin by answering your question and then proceed to paraphrase my statement.

You asked Dr. McGinnis what might be ways that this committee or anyone might be able to determine how a particular piece of research could bear upon prevention of disease. There are some general aspects which I will deal with in my summary testimony, but briefly they would say this: That one of your best guarantees is to make sure that research is excellent and carried out with the best possible technique, with perseverance and continuity. So that excellence in science is one of the first things you have to promote.

Mr. GRAMM. If I may just stop you there, how do we, as people who are engaging in making laws and not people who are at the National Institutes of Health looking over people's shoulders, promote excellence? How do we assure accountability in terms of research contracts that are granted?

Dr. FREDRICKSON. I think first of all you must assure and be reasonably reassured that a system of determination of technical excellence by peer review, unprejudiced and uninfluenced by improper influences, is carried out in the quality judgment relative to every proposal for scientific experimentation. I think we have that system at the National Institutes of Health.

I think we need to constantly monitor it ourselves and to be able to answer any questions you may have about it, and certainly to be reassured ourselves that it continues to function in that way. There really is nothing any of us can do who are not experts in a given area to be reassured that this is a proposal in a highly specific area that meets the best standards for the application of the scientific method to the testing of a hypothesis.

Mr. GRAMM. Continue with your testimony, Dr. Fredrickson. I just thought it was a relevant time to bring that question up.

Dr. FREDRICKSON. I think the second reassurance must be that this research that we have talked about, this excellence in science, goes on in a milieu which favors application when it becomes obvious that it may have any practical opportunity if further developed.

And third, this application needs to take place and be transferred rapidly to a system where applications, once demonstrated to be practical, are really promoted and used to the fullest extent in the practice of the art of healing and promoting health.

I say that because I have in mind three sets of experiences that have come to my mind in the last few weeks, which depend upon a finding for which the Nobel Prize was given 2 years ago in basic science relative to recombinant DNA. My guess is that at the time that research was going on, we never attributed that research to prevention in our attempts to give you an honest accounting of our efforts. Nothing could have been further from our minds.

But it so happens that those techniques today are on the verge of making possible the prevention of three diseases which are of great importance to us in this country and around the world.

There will come before the committee dealing with this problem in the next month the question of applying these techniques to the development of a vaccine for hoof and mouth disease, the dread disease of cattle which some say prevents the Third World from getting enough animal protein.

These techniques offer a possibility of a vaccine which would be more effective than has ever before been attempted. Another involves the NIH where there are ongoing efforts to isolate the rotovirus, which causes more deaths among children around the world from infantile diarrhea than any other single disease today.

Recombinant DNA techniques will probably make it possible in time to develop a vaccine, and it is possible that we might prevent those deaths. Prevention of that disease would have an enormous effect on the world, not only in this country but throughout all of the nations.

Also important is that these technique has already made it easy to understand the genomes which cause instability in the polio virus, that tricky virus which troubles us so much each year in our attempts to stay one step ahead in prevention programs by vaccination.

Now, all of these have come about because of basic scientific advances, which we could not have anticipated a few years earlier.

NIH is generally charged, as you know, Mr. Chairman, with carrying out research designed to improve the Nation's health. Basically, research is an instrument conceived and established by the Federal Government to use the scientific method to understand all we can about life, and to determine the relevance of that knowledge to human function and the life span and happiness of people.

Our product is knowledge, fundamental knowledge, knowledge about life, disease and malfunction. And our ultimate aim, the aim of all that research, is prevention, because that clearly is the most useful extension of knowledge in the field of health.

Unfortunately, our ignorance prevents a lot of prevention today. Therefore, we have to apply our mission in terms of learning more about treatment, the palliation of disease once it has occurred.

So we look for cures while we try to assess health status and to diagnose abnormalities. But underlying the whole thrust of that search for truth and for reality is a determination that we would like to be one step ahead of disease and prevent it.

Now, the NIH has been entrusted with the task of providing the data, information, and knowledge upon which many other important health activities are based. It is the primary instrument for bringing science into the practice of healing.

And there are three proscriptions about the boundaries of NIH which I would like to share with you, Mr. Chairman, because they bear on the questions that have already been raised in this hearing.

First of all, we think that NIH must not be a regulatory agency. The mandates of regulation make it difficult to be objective, and to carry out research without time constraints and with the serenity. A laboratory setting without other constraints that is absolutely necessary for the highest excellence in science.

The second is that NIH must not function to provide long-term continuing care for people except in relation to its research, because those obligations cannot be abandoned once you have accepted them. And if that should occur, what the Nation expects to use money for in terms of new knowledge would be sacrificed to meet care commitments.

The third point, Mr. Chairman, is that there must be some limits to the kinds of health promotion activities in which NIH is engaged. There is no question but that our job is to find out all that we can about the most basic things and convert them to the most practical advantage in extending life and relieving man of disease. But there are limits to the degree to which we can promote new techniques, alter the practice of medicine or, indeed, the behavior of American citizens with relationship to prevention of disease. And those limits are very hard to define. They lie somewhere out in the field somewhere between these boundaries.

Our job is not only to determine what we can about basic knowledge. We need to make it practical and we need to test in the field new inventions that have been conceived in the laboratory or very refined environments to see if they work.

Once that is done, our job should begin to become less, and there is a point beyond which it should be taken over by another. It needs to be taken over by another because an agency like NIH should not be wholly engaged in health promotion, when there is not, basically, a scientific question which it is attempting to solve.

Let me illustrate what I mean, Mr. Chairman. Our National Heart, Lung, and Blood Institute is aggressively pursuing high blood pressure across this country. I am glad to say that in a few weeks you will read about some, I think, very interesting and useful results from this program. It is doing so on the very edge of the boundary of appropriate activities for NIH.

I think what it is doing is appropriate, but here is what I mean by the problem. We believe that one should do something about blood pressure and use certain techniques to lower it. What happens if one of those things which is being promoted by the Nation's primary instrument for the scientific method suddenly discovers from some new quarter, from Transylvania or somewhere else, that one of the medicines it is using is causing sexual impotence? Who is going to investigate?

Where, then, is the objectivity? Where is the Nation's instrument for still pursuing the truth in this difficult world where you cannot anticipate all of the answers from the beginning?

Therefore, one of our institutions must not get so far committed to promoting its own inventions that it cannot remain objective about the long-range concerns of its effectiveness, its possible toxicity and all of these problems that inevitably arise.

I think that NIH should vigorously approach the boundary in terms of health promotion. We should devise ways to take these arcane pieces of knowledge and convert them into useful things in the doctor's bag. We should do everything up to the point, but I think we need to be complemented in the Public Health Service, in the medical profession, by Government and the private sector in using those facts we should not encumber our objectivity but rather be there to answer the next wave of questions which will arise

out of anything that is used, out of birth control pills, out of medications for high blood pressure, out of antibiotics. They all eventually come back with more questions for which there must be experts to seek the answers.

Well, Mr. Chairman, I have in my statement discussed at great length how we arrive at our priorities. Let me simply say that the Congress, in setting out the 11 institutes of the National Institutes of Health over a number of years, has in a way sectorized the whole field of biomedical research, behavioral research, into organ systems, into major diseases, I think very properly.

More laterally, it has constructed so-called noncategorical institutes. So we have work on the beginning of life, motherhood, pregnancy, childhood, birth. And now we have an Aging Institute, the last, one that I think will attempt that difficult experiment of bringing the social sciences together with the harder sciences in trying to understand the problem of an aging population.

I think that sectoring is very good, and we use that system at NIH to take advantage of that diversity. We recognize the difference of maturity of different parts of the field of knowledge. We attempt at central NIH to integrate the needs and opportunities, the possibilities, the aspirations, with emphases on promotion of health and prevention, and to give you in the annual hearings the best view we can of where we think the money should go.

We have mechanistic systems which we have arrayed according to priority settings. This year, Mr. Chairman, the health science agencies of HEW have been undergoing an intensive review of their own activities, and you see now more integration among these agencies—nine of them that carry out some kind of health research—than we have ever had before.

In my statement, or I can later discuss, if you wish, some examples of this kind of activity. I have also summarized there a number of instances of health promotion plans.

I can tell you roughly what the cost of our resources is in terms of activities which meet a definition of prevention of disease, or preventing the worsening of a disease that is already there.

But I think the main thing I wanted to get across to you is that the NIH has a mission of new knowledge, new knowledge that must come up to meet the needs of a whole system of people, a whole system for serving the needs of the people. In the use of the scientific method, I think there is no finer agency nor have we or anybody else in the world created a finer system for biomedical research today. But there are limits to the ability of the NIH, of course, to change medical practice in this country, or to necessarily make health prevention and health promotion work, even though we have many of the answers.

[Testimony resumes on p. 111.]

[Dr. Fredrickson's prepared statement and attachments follow:]

— STATEMENT OF DONALD S. FREDRICKSON, M.D.,
DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Mr. Chairman and Members of the Subcommittee:

I am grateful for the opportunity to come before you this afternoon to discuss with you my perceptions of the NIH and its role within the context of the health science enterprise. How do we set our priorities for the conduct of research in the health sciences? How do NIH's activities contribute to the Government's efforts to promote good health among the population and to prevent disease? I shall try to give you, in general terms, the answers to these questions as I see them.

The NIH is generally charged with carrying out research designed to improve the Nation's health. Its chief product is, therefore, knowledge and understanding of fundamental life processes, knowledge of how these processes may be altered and function improperly, knowledge of ways to correct the states of disease that may result, and, especially knowledge of ways to prevent the onset of disease and extend healthful lives. While all of these activities proceed ultimately toward the most cost-effective means of improving the health of the population, our current lack of knowledge requires us to continue to develop new methods of treatment for diseases not yet preventable. We cannot neglect those who are sick. Our ignorance still prevents us from preventing many diseases. So we must still seek cures and palliation. These, as well as the development of better measurements of health status and better methods for diagnosing abnormalities, must continue to join research toward prevention among the major missions of the NIH.

The Setting of Priorities for Biomedical Research

The NIH has been entrusted with the task of providing the data, the information, the knowledge, and the understanding upon which many other important health activities are based. NIH is not and should not be a regulatory agency, nor is its function to provide services to the sick or to practice medicine in any way except in relation to research.

In order to meet the ever expanding demand for knowledge most effectively and efficiently, it is necessary that the NIH carefully determine its priorities for conducting biomedical research. The NIH has instituted a formal planning process to make these important judgments.

In serially establishing the component institutes of NIH over the period 1936 to 1974, Congress has deliberately established a grid for the plotting of the Nation's priorities and progress in the life and health sciences. Most of the institutes are clearly identified as subtending sectors of knowledge concerning major diseases or organ systems. Relatively recently, non-categorical institutes were added for research on the beginning (NICHD) and the later years of life (Aging). Each of these institutes has two features directly related to priority setting. One is subdivision into various program offices and divisions. The second is a full-time planning staff to carefully examine and review the success of individual programs, and the need to create new ones, all within the constraints imposed by the annual cycle of the President's proposed budget and the Congressional appropriations process.

The public advisory council of each institute has from the beginning presented its own views on research priorities. In recent

years, the consultations between staff and council has greatly increased and the advisors' views are integrated with the recommendations of the staff often now in highly formal plans, subject to periodic update.

In recent years, the NIH has collectively decided upon new frameworks for discussing and projecting the allocations of its constituent institutes. Thus, there now recurs a process of synthesis and distillation in which each institute presents its case before the Director of the NIH in an intense annual review designed to bring out the needs and opportunities in each sector for the preparation and defense of annual budgets. The concerns of all of the NIH components are then integrated into an aggregate NIH research plan, in which the priorities of each are balanced and reflected in the image of the total research system supported by the institutes, a system upon which not only this Nation, but much of the world depends for meeting many needs for new knowledge. The aggregate NIH budget must also be adjusted to the available resources, and to the concerns of the public as expressed by both the Congress and the Administration. Just yesterday, I met for several hours with the staff from the National Institute of Arthritis, Metabolism, and Digestive Diseases, one of the largest institutes of the NIH, to discuss ongoing programs and future plans for the institute. And before January ends all 18 bureaus, institutes, and divisions of NIH plus seven cross-cutting or trans-NIH coordinating groups will have showed the same dialectic.

Beginning last year, and for the first time in the history of the Department, a review at lesser depth, but far greater breadth, was extended to the research activities of nine agencies comprising the total OHEW health research budget. The resulting analyses and

initiatives developed here will enhance efficiency and increase the coordination and complementarity of the Department's health-related research.

NIH gives the highest priority in its administration of health research to the stable funding of investigator-initiated research projects, the most laissez-faire of all the mechanisms yet subject to a lengthy competitive peer review process for quality control. Ideally, all research should be supported in a stable manner and, when possible, insulated from the fluctuations of the economy or the prevailing political winds. A second priority goes to its own excellent intramural programs. By seeking to stabilize certain levels of grant and intramural activity, we guarantee opportunities for the brightest and most capable investigators to explore ideas and develop new knowledge which will benefit us all. Yet, in special centers of many types, the ideas of other researchers flower, particularly in translation to clinical problems, and these mechanisms, too, have to have some protection.

Nearly as important as the stability of research funding is the continued support of research training. The turnover rate of biomedical scientists seems to be approximately 10% per year. It is necessary that the source of energy for research and of new ideas continually be replenished from a pool of highly qualified trainees with the skills necessary to maintain the high standards of the system.

Of great importance to the continuation of high-quality research is the maintenance of research resources. Obsolescence of the Nation's biomedical research facilities is becoming a serious problem, not only

at research institutes and universities, but here at the NIH campus. The Clinical Center and some of the research buildings are currently in need of major renovations. Thus, each year, we set aside a portion of our resources for this purpose.

An important aspect of this planning process is to recognize particular areas of biomedical research which merit special attention. Such topics may take on particular significance because of a new discovery, a new commitment on the part of our Nation's leaders, or a directive from the Congress. This last can be related to very practical problems, where work of a pedestrian character must be enriched by participation of those also in contact with the most advanced work and newest technologies. Here, meeting the needs of the regulators is often a common objective. An example is the National Toxicology Program, which includes the testing of substances for carcinogenicity. It is being given high priority for expansion in FY 1980 despite a generally austere budget construction. Research into the biological effects of ionizing radiation has also been a topic of great recent interest. There are both expanded research programs within the Department of Health, Education, and Welfare designed to assess the biological effects of ionizing radiation, and a new initiative to review and coordinate the entire scope of Federal research activities in this area.

Other priorities in the general area of special projects usually entail the development of a new clinical procedure or a new drug--the end stage in the long process of research and development where the

consumer at last receives the benefit of the years of labor. These programs may include a new therapeutic regime, a new method of detection for cancer, or a new procedure for preventing coronary heart attacks.

NIH sets priorities in at least two dimensions. One, the relative emphasis on different sectors is set more by Congress than NIH. Another is on mechanisms of scientific inquiry. Here, too, Congress has strong views, but the professional judgments of scientists and administrators play important roles, too. In mechanism terms, the priorities may be stated too simply.

The planning process for NIH, therefore, considers many scientific issues, as well as social, political, and economic factors, when setting its priorities for biomedical research. These considerations transcend individual diseases or specific health problems. And ultimately, the quality and productivity of the system depends upon the maintenance of a stable research enterprise.

NIH Programs in Health Promotion and Disease Prevention

Thus far, I have devoted my remarks to presenting a general view of the activities of the NIH, and its role in providing the knowledge base necessary to improve the health of the American people. Almost all NIH work ultimately enables us to promote health and prevent disease. However, an important component of NIH's quest for knowledge is the search for practical, immediate solutions to health problems. While it is important that NIH not extend its boundaries into health care delivery, there are, nevertheless, certain directed education and research programs that are appropriate for the NIH.

The National Heart, Lung, and Blood Institute has had considerable success with its National High Blood Pressure Education Program in achieving and documenting positive changes in hypertension control in the Nation. Initiated in 1972 and sustained each year since, this program has demonstrated that a major information dissemination effort can be effective in converting health knowledge into health action.

The Foods for Health Program of the Heart Institute, initiated in October 1978 in 90 Giant supermarkets in the Washington area, used large posters and a free publication to provide consumers with information about the relationship between diet and coronary heart disease. NHLBI is now working with the American Heart Association to bring the Foods for Health project to other parts of the Nation. In addition, NIH's Nutrition Coordinating Committee is considering a pilot project with Giant Food Stores which would deal with cardiovascular and other nutrition-related diseases.

The National Institute of Child Health and Human Development conducts and supports a variety of programs which exemplify the relationship between basic research and disease prevention. This Institute is looking at the pre-natal and neo-natal origins of disease and disability, so that problems that interfere with life and activity can be anticipated and prevented. For example, in FY 1979, the NICHD launched a new program of research in clinical nutrition and early development to study the effects of diet and other influences in childhood on the later development of such disorders as obesity, diabetes, hypertension, and heart disease.

The well-being of these and other prevention programs is inextricably tied to that of the NIH as a whole. These prevention activities are possible only after years of investment in basic research. Only after we have shed some light on the fundamental relationship between molecules, cells, human beings, and the environment, can the NIH speak intelligently to the American people about disease prevention or support a line of prevention research.

Conclusion

It is difficult for me to comment on where NIH will be going in the next two decades. It would perhaps be correct to say that NIH should always be doing primarily what it does now; that is, provide the principal support for biomedical science in the United States. The topics which scientists investigate will necessarily change, but it is not the sole prerogative of the Government or NIH to specify what these subjects must ultimately be. They will be determined through the process of accretion of knowledge a step at a time. As we learn each new fact, perhaps ten more areas of research will be suggested. As these research findings allow us to conquer and prevent certain diseases and health problems, we will become aware of new ones or aware that at least old ones are now within our control. It will be through a harmonious relationship between the Department and NIH, and Congress, all working toward the same goals, that we shall be able to continue our history of excellence long into the future.

This concludes my remarks, Mr. Chairman. I will be happy to answer any questions you or your colleagues may have.

National Cancer Institute

- Testing of chemicals for carcinogenicity
- Development of improved methods for predicting carcinogenicity, mutagenicity, and teratogenicity
- Investigation of cellular and molecular mechanisms of carcinogenesis
- Development of chemopreventive agents; Immunopreventive techniques
- Development of improved animal-to-man extrapolation techniques
- Educational programs to reduce exposure to occupational hazards
- Diet, Nutrition, and Cancer Program
- Smoking cessation research, education and information programs; identification of high-risk groups
- Studies on how to apply etiologic information
- Environmental carcinogenesis research, information and education programs
- Studies of radiation exposure and cancer
- Studies of Vitamin A derivatives as preventive agents
- Epidemiologic studies to determine high-risk groups and individuals as well as etiologic factors for cancer
- Studies on the economics of specific prevention activities (cost/benefit)

National Heart, Lung, and Blood Institute

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- Community-based multiple risk factor intervention demonstration programs
- Smoking cessation research, education, and demonstration programs; identification of high-risk individuals
- National High Blood Pressure Education Program
- Research, information, and demonstration programs aimed at control of hypertension
- Prevention of deep-vein thrombosis
- Education and counseling programs for Sickle Cell Disease
- Nutrition research, education, and demonstration programs aimed at lowering cholesterol, blood lipids, and weight levels
- Research into application of behavioral science to control of heart, lung, and blood disorders
- Epidemiologic studies

National Institute of General Medical Sciences

- Investigation of hereditary factors which contribute to many major diseases
- Research into the cellular and molecular basis of disease
- Research to improve the safety and efficacy of drugs; Investigation of toxicologic problems and the interaction of drugs and environmental factors
- Prevention of death and disability due to injury, burns, shock, and trauma

National Institute of Neurological and Communicative Disorders and Stroke

- A world-wide epidemiologic survey and investigation of the causes and relationships of aging disorders
- Development of vaccines for chronic infections of the central nervous system such as cytomegaloviruses, herpes, and toxoplasmosis
- Identification of factors, such as smoking and alcoholism, associated with high incidence of laryngeal cancer
- Studies of the epidemiology and underlying mechanisms of speech and language impairment in children before admission to school
- Studies of the underlying mechanisms of Sudden Infant Death Syndrome (SIDS)
- Studies of infantile febrile seizures as possible predictors of epilepsy
- Research on slow transmissible viruses, which cause chronic noninflammatory central nervous system diseases

National Institute of Neurological and Communicative Disorders and Stroke (Continued)

- **Studies of lysosomal storage diseases to intercept the development through counseling and prenatal diagnosis**
- **Studies of otitis media in children in relation to hearing loss, language, and cognition disorders**
- **Studies on the role of platelets and the use of aspirin in preventing transient ischemic attacks (TIAs)**
- **Epidemiologic studies to determine risk factors and antecedents for neurological and communicative disorders**
- **Research on the anatomical and physiological effects of noise and noise induced hearing loss**

Primary Prevention Funding at NIH
(As a Percentage of Total Institute Funds)
(FY 1978 Obligations in Thousands)

Institute	Grants		Contracts		Intramural		Total	
	Total ¹	Prevention %	Total ¹	Prevention %	Total ¹	Prevention %	Total	Prevention %
NCI	\$396,703 ²	\$43,218 10.9	\$273,182 ³	\$52,202 19.1	\$91,089	\$13,691 15.0	\$760,954	\$109,111 14.3
NHLBI	276,487	35,624 12.9	90,073	20,508 22.8	35,002	2,184 6.2	401,562	58,316 14.5
NIA	21,955	4,123 18.8	1,979	238 12.0	7,870	2,251 28.6	31,804	6,612 20.8
NIAID	95,477	7,580 7.9	16,240	7,840 48.3	32,278	7,020 21.7	143,995	22,440 15.6
NIAMDD	187,590	3,516 1.9	12,736	442 6.8	34,153	985 2.9	234,479	4,943 2.1
NICHD	107,293	51,524 48.0	20,358	16,707 82.1	18,728	2,193 11.7	146,377	70,424 48.1
NIDR	34,971	2,516 7.2	4,830	993 20.6	12,330	874 7.1	52,131	4,383 8.4
NIHNS	32,513	28,780 88.5	6,235	3,945 ⁴ 63.3	17,570	9,160 52.1	56,318	41,805 74.4
NIGMS	174,693	2,326 1.3	893	0 0	379	0 0	175,905	2,326 1.3
NINCDS	111,876	12,436 11.1	16,567	4,151 22.4	27,574	5,360 19.4	158,017	21,947 13.9
NEI	64,754	2,955 4.6	4,922	1,316 26.7	7,905	409 6.1	77,641	4,760 6.1
DDR	135,797	4,974 ⁵ 3.7	4,128	0 0	0	0 0	139,925	4,974 ⁵ 3.6
Total/%	1,840,109	199,572 12.2	454,143	108,342 23.9	284,916	44,207 15.5	2,379,168 ⁵	352,121 14.8

1. From table "1978 Actual Obligations (New Mechanism Structure)" (Revised 2/3/79), Division of Financial Management, NIH.

2. Includes "Disease Control" appropriations.

3. FY 1977 funds.

4. Includes \$2,220 in Interagency Agreements.

5. Total FY 1978 NIH obligation, including FIC, training, and management, was \$2,926,014.

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Primary Prevention Funding at NIH (FY 1978 Obligations in Thousands)

	Grants		Contracts		Intramural		Total	
	No. of Projects	Prevention ¹ Funds	No. of Projects	Prevention ¹ Funds	No. of Projects	Prevention ¹ Funds	No. of Projects	Prevention ¹ Funds
NCI	460	\$43,218	217	\$52,202	NA	\$13,091	677	\$109,111
NHLBI	318	35,024	82	20,508	41	2,184	439	58,316
NIA	39	4,123	1	238	18	2,251	58	6,612
NIAID	108	7,580	87	7,840	26	7,020	201	22,440
NIAMDD	31	3,516	4	442	13	985	48	4,943
NICHD	508	51,524	198	16,707	8	2,193	714	70,424
NIDR	30	2,518	16	893	25	874	71	4,383
NIEHS	234	28,780	22	3,845 ²	91	9,160	347	41,885
NIGMS	14	2,326	0	0	0	0	14	2,326
NINCDS	383	12,436	38	4,151	49	5,360	470	21,947
NEI	32	2,955	22	1,316	2	489	56	4,760
DRR ³	317	4,974	0	0	0	0	317	4,974
TOTAL	2,472	199,572	667	108,342	273	44,207	3,412	352,121

1. Estimates by individual Institutes.

2. FY 1977 funds.

3. Includes \$2,226 in Interagency Agreements.

PRIMARY PREVENTION REPRESENTS LESS THAN 1% OF TOTAL NIH FUNDING FOR BIOMEDICAL RESEARCH

SIX NIH INSTITUTES MAKE UP 92% OF ALL PRIMARY PREVENTION SPENDING

NCI-----31%
 NICHD-----20%
 NHLBI-----16.6%
 NIEHS-----11.9%
 NIAID-----6.4%
 NINCDS-----6.2%

ONLY 4 INSTITUTES SPEND MORE THAN 1% OF THEIR TOTAL BUDGET ON PRIMARY PREVENTION

INFORMATION SHEET

SMOKING

- Nearly doubles the risk of heart attacks for men
- Ten million Americans suffer from smoking-related chronic disease
- 320,000 premature deaths per year are associated with smoking
- 4000 children and adolescents become smokers each day
- One third of all 18 year olds smoke
- If all Americans stopped smoking there would be 30% fewer coronary deaths per year with 200,000 lives being saved each year
- Lung cancer has increased 10 times in women since 1930 and is now the 2nd leading cause of cancer deaths in women. In 1963 it was the 8th cause of death. The rise is associated with increased smoking by women.

ALCOHOL

- Is a contributing factor in 10% of all deaths
- Is involved in 1/4 of all traffic accidents

Occupational Risks (exposure to toxic chemicals etc.)

- Up to 20% of cancer death may be associated with occupational risks
- Each year, 100,000 Americans die from occupational illnesses
- Almost 400,000 new cases of occupational diseases are recognized each year

LIFE EXPECTANCY

- The Japanese and Italians have a greater life expectancy than Americans at all ages
- 14 other countries have a longer life expectancy for men and 6 other countries have a longer life expectancy for women

OTHER COMPARISONS

- 12 other countries have a lower incidence of cancer deaths than the US
- 26 other countries have a lower incidence of cardiovascular disease deaths
- 11 other countries have a lower infant mortality rate

(From the Washington Post, Thursday, Nov. 3, 1979)

MORE WOMEN DYING OF LUNG CANCER

NEW YORK.—Lung cancer has become the number two cause of cancer deaths in women, second only to breast cancer, and by 1983 will pass breast cancer to become the leader, according to the American Cancer Society.

This is happening at the same time that a woman's chance of developing breast cancer also has increased.

The reason for the sharp increase in lung cancer in women is the sharp rise, going back to the 1940s and 1950s, in women's cigarette smoking. More women smokers are now reaching middle or later life, when lung cancer strike.

Lung cancer deaths in women passed cancer of the colon (large intestine) and rectum in 1977, but the statistics have just been compiled and reported by the society. The projection to 1983 was made by U.S. Surgeon General Julius Richmond and will be announced by Deputy Surgeon General John Greene here today.

In 1930 the annual lung cancer death rate in women was only 1.5 per 100,000 while there were 21.4 deaths from breast cancer.

In 1977 there were 14.9 lung cancer deaths per 100,000 women while the death rate for colon and rectal cancer was 14.3.

The breast cancer death rate has remained virtually the same over the years—sometimes rising a little, sometimes falling a little, then rising again despite advances in treatment.

A newborn baby girl in the United States now has one chance in 11 of having breast cancer during her life, compared to the previously accepted lower risk of one in 13. No one knows why. Among leading suspected causes are increased fat and protein in the diet and increased exposures of women to industrial and environmental chemicals.

In lung cancer, what's happening to women is what happened to men a few decades after men in large numbers began smoking cigarettes. Lawrence Garfinkel, Cancer Society statistician, explained. In 1963 lung cancer ranked only eighth as a cause of female cancer deaths.

Mr. GRAMM. Thank you, Dr. Fredrickson.

The Chair would now yield to the gentleman from New Jersey.

Mr. MAGUIRE. Thank you, Mr. Chairman.

Dr. McGinnis, you have been one of the leading advocates in the administration for prevention, and I wonder, in view of the discussion we have had this afternoon with previous witnesses, and now with yourself and Dr. Fredrickson, if you would give us your views of the question of the advisory councils, the peer review process, offices of the directors with respect to the strength at that level on the prevention issue, and the larger question of leadership in this area.

Dr. MCGINNIS. Let me deal with each of those in turn, if I may: The question of peer review councils, those of prevention-oriented people in the directorships of the various institutes, and the overall leadership.

First, it was the feeling of the participants in the departmental task force on prevention, which began, as I mentioned, 2 years ago, that one of the things that might be undertaken in the research area, one specific focus, was on development of the knowledge base of prevention.

And one of the recommendations of that group was that the National Institutes of Health begin to look a little more extensively at the way in which the sensitivity to the needs of epidemiologic studies, studies that were more oriented to the prevention of the disease, might be incorporated into the study sections' activities. I think the National Institutes of Health has been responsive in that regard or is moving to become more responsive in that regard. You have heard from Dr. Wynder that both the National Heart, Lung,



Proceedings
of the 1979
Meetings of the
Chairpersons
of NIH Scientific
Review Groups

Prepared by:
Division of Research Grants

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I. INTRODUCTION

Over the years there have been few opportunities for members of National Institutes of Health (NIH) scientific review groups (SRGs) and representatives of the NIH administration to share their concerns and suggestions for refinements in the grants and contract peer review process. To promote such interaction, the Associate Director for Extramural Research and Training, NIH, scheduled four meetings, on November 19, November 27, December 3, and December 13, 1979, with the chairpersons of all the NIH SRGs.

Besides the chairpersons, the following NIH representatives were present at these one day meetings: Dr. Donald S. Fredrickson, Director; Dr. William F. Raub, Associate Director for Extramural Research and Training; Dr. Carl D. Douglass, Director, Division of Research Grants (DRG); Dr. S. Stephen Schiaffino, Deputy Director, DRG; Dr. Samuel M. Schwartz, Associate Director for Scientific Review, DRG; the executive secretaries of the SRGs; and selected administrators from the various bureaus, institutes, and divisions (BIDs). (A complete list of participants, except for BID staff, is included in Appendix A.) To provide a more conducive atmosphere for a free exchange of ideas, about 25 chairpersons were invited to each meeting.

Agenda items were chosen from topics of interest that had previously been solicited from the chairpersons and other scientific review group members. The basic format was as follows:

- 10:00 a.m. to 10:15 a.m.
Opening Remarks and Introductions, Dr. Douglass
- 10:15 a.m. to 10:30 a.m.
"Current Issues in Peer Review," Dr. Raub
- 10:30 a.m. to 12:00 Noon
Roundtable Discussion, Drs. Raub, Douglass, Schiaffino, Schwartz, and Chairpersons
- 12:00 Noon to 1:00 p.m. -- Lunch
- 1:00 p.m. to 2:00 p.m.
"The Status of Biomedical Research: NIH Perspective,"
Dr. Fredrickson
Roundtable Discussion, Dr. Fredrickson and Chairpersons
- 2:00 p.m. to 2:15 p.m. -- Break
- 2:15 p.m. to 3:00 p.m.
Roundtable Discussions, Drs. Raub, Douglass, Schiaffino, Schwartz, and Chairpersons

To avoid repetition and to increase clarity of presentation, the proceedings of the four meetings have been merged here into a single volume.

The chapters on "The Status of Biomedical Research: NIH Perspective" and "Current Issues in Peer Review" are composites of Dr. Fredrickson's and Dr. Raub's presentations at the separate meetings. In the last chapter pertaining to the roundtable discussions, the unstructured discussions have been organized into subject areas. Because it was impossible to identify the majority of the speakers, the roundtable discussions have generally been divided into anonymous comments or questions from the various chairpersons and responses from the NIH staff members.

II. THE STATUS OF BIOMEDICAL RESEARCH: NIH PERSPECTIVE

Dr. Donald S. Fredrickson, Director, NIH

It is a pleasure to welcome you to NIH, and I want to express my own personal gratitude for what you are doing. You are the vanguard in a way, but you are also the rock of stability upon which this whole system rests.

This has been a very busy year. We have been in the middle of a health planning exercise for some time and have gone now from principles to proposals. Some of you perhaps have read the principles, which were signed and sent out by the Secretary of HEW. You will note that the first statement was an acknowledgement that the support of fundamental research was extremely important and that Department funds should be expended on the basis of criteria, the first of which included a judgment of scientific excellence as determined by peer review.

I hope that this report is released for your perusal very soon. It would give you a chance to see what we've been thinking about. Much of it has to do with looking at the research activities of the Department as a whole. NIH, by far the largest and the oldest of the research organizations in HEW, nevertheless is joined by eight to nine other agencies that also conduct research and have many different needs, and whose demands for participation in the knowledge market are important today to a large number of constituencies.

We have before the new Secretary a second report which will deal with a certain number of proposals. One of these proposes that the Congress and the Administration look at what it would take to put a floor on the number of research projects that are supported annually for the next 5 years.

Some traditionalists think this is foolishness. They feel that this proposal will lead to self-fulfilling prophecies, that it interferes with an old equilibrium between the Administration, which says "no," and the Congress, which has always said "yes." But we're concerned that the delicate balance, which is so timed and tuned to perfect and predictable responses, may go wrong. Thus we are advocating a stabilization of support for research grants, if we can get the Congress and the Administration to be mutually interested. At the same time, we are recognizing that if you stabilize support, then the other parts of the system must be adjusted in some way as well, either up or down, and the costs of that in terms of program and the nation's capacity for scientific inquiry will have to be reckoned with.

In the first week in December, the Director's Advisory Committee will sit around this table. That Committee, as with the councils, includes all kinds of people interested in and knowledgeable about science, from both the lay and technical sides. We'll talk about "what if," using these new allocation rubrics that we've devised here to look at the NIH, and present the research picture of the country as clearly and crisply as possible.

This is all related to activities we started many months ago, trying to use a new way of aggregating our resources so that they reflect some kind of functional modes along the continuum that is biomedical research, trying to speak a common language and trying also to draw into collective judgments many of the activities that heretofore have been called NIH only because we added up what each of these wonderful and individualistic institutes decided to do.

One example is the manpower development program. Up to about this year it was not clear what the NIH program was. But it is becoming very clear this year that a greater degree of collective decisionmaking and integration can make quite a difference in, for example, just the Career Development Awards. We had some 25 kinds I think until very recently when we came back down to a far more limited number of rules and codes that institutions should have to remember in order to apply for this kind of support.

This year we have added a number of consultants to the Director's Advisory Committee meeting. One of the features at this particular meeting is that one of your members, a study section chairperson, will tell us what he thinks about public participation in setting priorities in science. We want to examine, to get some thoughtful understanding among ourselves about, the limits and the capacity of that kind of participatory activity. Acknowledging that it's extremely important, that it's quite defensible, that it's desirable in an enterprise that is paid for by public funds, we nevertheless recognize that there are limits to which it can be done effectively and efficiently. This is one of our most important quests during the next several years. You are all aware that there is a bill before the Senate, called S. 988, which proposes that study sections include lay representatives, that is people who are not trained technically. I think this is an item that will be widely discussed during the coming year in various hearings and will possibly appear on legislation.

Probably there's not been any time in recent history when peer review has been under more pressure. The funding ratio in terms of the approval rate has been dropping this year, and things will not be easier in the next year or so. Already there have been some reproaches to the system even in the Congress. But we have informed those Congressmen who particularly like to schedule hearings relative to the peer review process that they may look forward to an even busier next year if NIH can only fund a third or less of the grants.

The call recently by a member of Congress for a GAO investigation of the peer review system because it was "obviously not fair" to a particular area of science was actually welcomed by us. We would be delighted to have Congressmen here so we can tell them about the number of study sections we had 10 years ago and the number we have now, the change in the number of grants, and the workload.

Certainly there are many questions we have for you as study section chairpersons that I wish I had time to explore with you, and I hope that you will take them up during the rest of the session here today. I'm particularly interested in your attitudes about whether you can make the fine distinctions that are necessary and how valuable you think those distinctions are when you are discussing a very large number of grants, the majority of which might not be

funded. The questions of salaries for investigators, overhead, and so forth are very much on our minds these days as are, of course, many correlative activities, such as training and the whole issue of grants versus the rest of the system.

NIH has this year tried to look first at the R01* and the P01** mechanisms, stating publicly and without any qualms that these are our first lines of defense in any period of severe austerity. But we're also aware as we propose certain formulas for grant support, whether it be in terms of priority scores or percentage of approved applications that might be funded, that when we do that we're putting intense pressure on other parts of the system as well.

All in all, things are going very well. I think we have in the last couple of years managed to define the limits of NIH and to find acceptance of those limits among the people with whom all of us have to deal and upon whose attitudes much of this enterprise depends. We have stayed out of regulatory activities. We still aren't burdened by long-term commitments to the care of populations. And so far, I think we have begun to see a yielding in the area of excessive health promotion. In fact, we have been among the strongest voices urging the creation of a stronger health promotion agency, which will take additional pressure off us not to engage in activities that, like regulation, could interfere with our objectivity.

I think the apparatus for science is healthy. But it also is not going to be very obese during the next few years, and keeping us lean and muscular in exactly the right places is a responsibility we take very seriously. Throughout that whole process, nothing comes up in fundamental importance to the activity which you are responsible for. On peer review hangs the whole game. And upon you lie many burdens. Since I last met with 30 study section chairpersons, we have four new study sections; but that was one Secretary ago, and we are required to begin again to acquaint a new administration with why we want more consultants and so forth. We're tireless, and the subject remains very important to us. But I can't stress the requirement of time and effort that is required on both sides when an administration very quickly changes. All the things that make daily business so easy have to be recreated. We have to learn to understand and to trust each other, and now we're proceeding back through that process.

The main thing I want to say to you, as I have said to other groups who have been here, is that the peer review system is not perfect, but it is the best system that exists. If there should be changes in it, I hope those changes will not be dramatic variations produced by just a few people affected by the system, but that they reflect the majority of those who understand and participate in the peer review system.

* Research project grant

** Program project grant

I think that you should be prepared this year for a number of questions about peer review, and it is not for us to orchestrate your response. But don't be afraid to come out of the great silent middle of science to defend, even in Congressional hearings or elsewhere, the nature of the system that is the subject of your meeting here. I will stop here and try to answer any specific questions you may have.

III. ROUNDTABLE DISCUSSION ON THE STATUS OF
BIOMEDICAL RESEARCH: NIH PERSPECTIVE
Chairpersons and Dr. Fredrickson

Question: I would like to comment on your observation about the hearings, specifically the criticism of the peer review system from within the scientific community. There seems to be relatively little coming out of that same community in defense of the system. Could you comment on that? What can be done?

Dr. Fredrickson: It's very difficult to get the great solid middle to move out, to take positions, and to make very clear where it stands. Clearly, if disaffected grantees or grant-seekers, and I understand their agony, want to have a public audience and get a member of the Congress to propose certain changes, that may be very well. But changes such as opening up study sections completely, changing the identification of innovative research, manipulating membership, or whatever shouldn't be made until we know that the majority of scientists concur. If the majority of scientists believe something should be done, I'll go along with it, because you have great wisdom, and I believe you completely in that sense. But that's the problem. You've got to see that the great middle comes out.

I'll give you one example of how effective I know that can be. When the first bills came out to regulate DNA by statute, we projected the bills on slides before 25 leaders of the scientific community. Everybody read silently about the \$10,000 a day fine that would accumulate every day there was a violation and so forth; and without our attempting to orchestrate anything, there occurred an outpouring from the universities and from the scientific societies and communities, a very adequate demonstration of what people thought and how extraordinarily effective they could be if they had a just cause as they saw it.

The same is certainly true of peer review. The system is not perfect and has problems, but we are maintaining the ability of the young to enter the system. We think that's very important. We also want to be sure that there's adequate representation of minorities and women. Many things have to be done to move with the times, but at the same time, there are some verities about this system, which all of us believe in. It works. It's never had a major scandal in 35 years of handing out tremendous sums of money to a community that has been the participants. It's a superb example of how democracy can really work. It's not perfect, but it's much better than anything else that has been proposed.

Question: Could you comment more about the proposal of putting a floor on the number of proposals?

Dr. Fredrickson: In each of the last 3 years, the House Appropriations Committee has wanted to increase the NIH budget because the Administration had left it about flat, and they have arrived at their own way of doing that. The method has revolved almost completely around the research project grants. They know a lot about the system, and they like to think about ROIs. ROIs are not the only way to do research, but the creative opportunity for the investigator to get his or her own idea out, to be judged by the peer review system, is more than just aesthetically appealing. It is, I think, a first line of defense.

But they've been looking for a formula. Faced with problems about allocating scarce monies, they want to know how to do it. One year they will decide to fund up to a certain priority score. You know what a disaster that turns into when some scores are normalized and some are not. Or they may decide to pay a percentage of approved grants. The trouble is that market conditions are not predictable or stable, and the number of grant applications keeps increasing.

So last year the Congress, with our help, considered an alternative. How many renewal and competing grants do we award each year? It turns out to be something like 5,000 right now. The number concept appealed most to the two committees last year; and we believe we ought to try to build on that, because that means you keep a certain number of people in business and can adjust the budget for inflation, and so forth. No formula is desirable. I agree with that. But these are not normal times as far as I'm concerned in predicting the budget.

Comment: I think we would all agree that the peer review system has functioned gloriously in the past. But I have grave reservations as to whether it can continue to do so in the future, if indeed the budgets are as restricted as you suggest. I think the capability of the peer review system to discriminate among the top 10 percent of the applications is far less than its ability to discriminate between the top and bottom halves. And if the situation really comes about where you're paying less than a third of approved applications, I wonder if the system isn't going to have to be modified in some way to make it more responsive in that upper third. Otherwise it becomes like a game of Russian roulette if the budget is that restricted.

Dr. Fredrickson: You are quite perceptive, though I don't know that we're necessarily going to be paying like that. I just want you to know that these are all possibilities. If we do that, I think you are absolutely right; we will have to adapt the current system in some way to make it as fair and as equitable as possible, and we'll need your help. We'll need your ingenuity in perceiving how that might be brought about. I don't think we can leap that far right now, and we won't really know our budget until the late spring anyway.

Question: Could you elucidate on the process of developing priorities? I think this relates well to the budget.

Dr. Fredrickson: Everybody asks science to set priorities. You have to do that; there never is enough to go around. Within NIH we have ways to set priorities which are entirely our own. Congress, by making 11 institutes, devised a grid presenting some priorities and then proceeded to make some bigger than others. This is perhaps wise, perhaps not, but still an excellent way for oversight by laymen using labels that are understandable by all. You should be aware that at NIH we're now organized programmatically. As I have often said before, we turn all the taps on full, wide open, and we let the water level, that is the priority score and the money, determine pretty much what comes out.

The question is whether if you really get into problems, you turn some of the taps tighter than others. These are the so-called program relevance decisions, some of which are made right now. They are not very severe, but we're insisting the institutes start to consult with their councils if they're going to talk about moving money around on a basis other than peer review. They must get constituency opinion and do it with consultation.

This type of priority setting doesn't have to operate very much today because many priorities have been set in the past by Congress through special mandates. But Congress is growing tired of mandates and much prefers to deal with the grant package. I understand that; they don't want to pretend that they have a higher wisdom about pushing cystic fibrosis as opposed to some other disease. So if Congress begins not to take these disease priorities too seriously, except in the institute budget, it will look more at instruments, which is a good thing to do when funding is tight.

The number of priorities you have to set are determined very much by the available amount of total resources. We are aware of some of the problems, but many mechanisms and operations are not in place at the present time because it has not been necessary to use them.

Question: In the national research establishment there is a partnership between the universities and the NIH, and the universities, a couple of fine universities, are in trouble, as much trouble as is the NIH. There's going to be terrific pressure to try to recover more salary support from grants and to increase indirect costs. Are you getting enough help in your battle with Congress from universities and vice versa? Is the partnership functioning as a partnership or are you functioning at cross-purposes?

Dr. Fredrickson: You have put the question in an awkward way, because I am not supposed to battle or call upon the forces from outside to do battle against the President's budget, and you know that.

Question: Do the NIH and the universities understand each other?

Dr. Fredrickson: Fairly well. We try to make sure somebody from the university is in the grants office, and the vice presidents are with us all the time so they can remind us of the current stresses. Do the universities understand the political process? Their representatives in Washington clearly do, but many do not.

I think our communication lines are pretty good, as open as they can be. We realize that the universities are essentially in a life struggle. They're not dying, but this is a tough business. I also have a feeling that no matter what NIH or the Government did, the universities would adapt. They're the most adaptive organisms in the world, like amoebas. You have to be like that.

The answer to your question is that it will probably have to come down to confrontation on certain specific issues. We've had confrontations with the universities, not entirely of our doing but very real, in the audit problems of the past decade. Many university bookkeeping systems are unsatisfactory, even though the Government asks much too much trivia. Both admitted it once. Many universities are working very hard at putting what resources they can into their bookkeeping systems, and we've tried to work it out by compromise.

Clearly the NIH recognizes its key importance to the universities. It can't do its mission without them, so there's no struggle between us that need occur. But there will be struggles between us and between departments, centers, deans, professors and investigators at universities, and most importantly between administrations and scientists, if the matter of overhead begins to get out of hand, if it becomes too large a fraction of the grant. Yet none of us fail to recognize the importance and fairness of overhead.

As the number of Government sources for funding or private sources decrease, people seek to get funds from the government. Yes, we'll have some more confrontation.

Question: Do we know the number of research positions that are available in this country and the half-life of an investigator?

Dr. Fredrickson: The half-life of a person in the NIH system, if we take the cohort study beginning in 1966, is 5 years. That's a shocking metabolic rate. That doesn't mean they've left research; you can obviously imagine the number of things they are doing. But the turnover is very high. We try to stress to all those who have to make political decisions about science that its vitality is utterly dependent on a continuing tie to the young. We know that. We didn't know how serious it was though. We had some illusions that we would last forever.

Concerning your other question, we don't know how many research positions are really available now. There is no index that can tell us that. We know that the number is very high, which seems to justify a continuing increase in the amount of training, but we're not sure what the hard core of vacancies really mean. We are extraordinarily limited in collecting such data, as you may or may not know. We can't ask something of more than nine people without an extensive procedure through the OMB*, and it usually isn't worth the trouble. The Academy**, however, can do otherwise.

Comment: Part of the commitment involved from either Government or society depends upon the perceived need. I would like to hear your comment on whether there is a role for the NIH to educate the citizenry about certain diseases as a way of developing support.

Dr. Fredrickson: I don't think you can ask the NIH to bear the burden of educating the population either to the needs of certain health problems or, more particularly, to the real meaning of science. Far too few citizens know enough about the scientific process to be able to engage in the debate, to cope with the questions that have to be answered about science in a democratic society where the public is supposed to take an active role.

Last week I was at a hearing of the Congress where I heard several of my colleagues unhappy with the NIH because it had not trained the medical community to understand prevention, and presumably it had not educated the whole population to accept the administration of prevention. Well I like to think NIH is a lot to all people, but it can't possibly be responsible for this. In fact, we want to get out of the health promotion business except where there are scientific questions that we can answer.

* Office of Management and Budget

** National Academy of Sciences

We have three very strong boundaries. One is that we cannot do regulatory activity. The second is that we are very cautious about health promotion. We have to do things right to the edge of practicality, but once it is established that something works in the field, we should not be out there selling it. Both of those activities, regulation and excessive health promotion, are very risky to your objectivity. The third is that we must not engage in long-term care or share commitments that go on endlessly, because that's the immediate source of hemorrhage for research money.

Those boundaries prevent us from going out and trying to sell the people on what we need. You have to do that. Of all the institutions in the country, the university has been the primary one to educate the people they send out and, to the limits of science, to give them optimism, some belief in the perfectability of the system. Our job today is trying to convince a very small but very important segment of the population, members of Congress and others in the Administration, about these facts.

Question: I would like to raise a question that you touched on briefly. Fundamental to the whole peer review system is the quality of the review, and there are several factors that during my period on study sections over the last 5 years have begun to put stress on that quality. One is the desire for broad representation in the review process, broad in the geographical sense, in the representation of women, and in the representation of minorities. Secondly, I think there are certain stresses that come from an increased workload, not just a large number of applications, but the increasing burden that disclosure stipulations have placed upon this process. Third, which we just touched on before you arrived, there is a noticeable lack of incentive for people to participate in these programs. What do you see as a future for avoiding possible problems? Do you in fact think they are real or potentially real?

Dr. Fredrickson: I think these are real problems. You have experienced in 5 years many changes and an increase in the tension of the review process. These problems, and there are others, will not go away, but we have to find ways to accommodate them, to adapt to them, to embrace them, to make sure that the process is enriched by them, and, for those that seem more burdensome, not to permit them to destroy the process.

I don't need to go into these very specifically unless you want to. The issue of affirmative action is a very strong one. I think it is legitimate. It is inescapable, but I think it is appropriate. One probably finds no disagreement about that.

The figures that we have today -- 17 to 20 percent women in our study sections, about 6 percent minorities -- are interesting. Both figures are much greater than the number of participating women or ethnic minorities in experimental science as best we can tell, and I am quick to say that the base is pretty soft. We really don't know precisely what the figures are, but this is the result of a conscious effort on the part of the Department to do something. But you know the figures before that were pretty scandalous if you look at them -- 1 percent, or 1/2 percent -- hardly justifiable. That is only 6, 7, 8 years ago. So I think some inequities have been addressed. There is justification for the changes.

It is necessary for us to explain to people whose objectives are different that some adjustments have to be made and on a long-term basis. Study sections just don't include 12 people, and you cannot afford to put a couple of other people on who really may be too immature or not understand the process. You can't do that because they are all specialists whose specialties add up to a field of activity of a study section. I don't think that the Department or any people involved are opting for that, but they are going to keep up the pressure, and I think that until we see the quality of review destroyed, we should not be too concerned.

I don't think it has been. I hope that we can accommodate this need to broaden and to bring into the mainstream of science in every way as many women and as many minorities as possible. I think we need the richness of their contributions. One of those activities is to participate in study sections.

The issues of disclosure are quiet. The threat produced by the Freedom of Information and the Privacy Acts of a couple of years ago are today far less exciting. Energy has gone out of those electrons and we are in a pretty stable position. Perhaps there will be some new court decisions, something else we have to adjust to, but I am fairly pleased with the stability as of this moment.

What is really the problem, of course, is the workload. There is a terrible attack on quality. You already give a tremendous amount of time, uncompensated in terms of money, to a load that is now simply too big for many study sections. All of us have to watch the market very carefully over the next couple of years. Then I think we need to find out, with your help, whether there are some adaptations, some aspects of review, that we need to put into place to keep the situation under control.

Comment: Many of the considerations of our study sections have not been on the question of maintaining the quality of science but maintaining capital equipment. We are finding it very difficult to rationalize the necessary constraints of capital equipment. In our particular discipline, people in very capital intensive areas of investigation are going away from academic research into industry because there is better equipment available to them in industry. I think this is an issue that really needs to be attacked. You can't keep things first-class in a research organization with an ever decreasing, outmoded equipment base.

Dr. Fredrickson: We recognize that we have a real problem in trying to replace equipment, and we are probably going to have to take direct measures, perhaps collective ones through research resources and perhaps in combination with the National Science Foundation. Last year for example, GMS* put seven million dollars into equipment. They had some extra money, and that was an excellent move, but unfortunately it was a single year capitalization.

There is also a problem in the institutions with sharing equipment and with maintenance. Years of affluence have left a fair fragmentation of support in individual laboratories and institutions and destroyed the incentive for collective activity to make sure that equipment was used as normally as possible.

* National Institute of General Medical Sciences, NIH

I know the problems and we can go further. NIH's own intramural program ought to develop a huge base for renting equipment. So if you want to buy a big piece of equipment, NIH will buy it for you, rent it back to you, and maintain it; but as soon as you are not using it, we will put it with somebody else. A few institutions are big enough to do that too. There are needs for reform in instruments that need to go along with improved capitalization.

Question: Dr. Fredrickson, could you comment on the future levels of enthusiasm to support training grant programs and more specifically on the types of proposals that are being considered to attract more M.D.'s into this area?

Dr. Fredrickson: On the first part of that question, the level of enthusiasm is very strong around here. We are now putting about 5 percent of NIH's total resources into training. That is not the total amount that is going into manpower development, but it is the amount basically going into training grants and fellowships of the conventional type. This 5 percent in our estimate, albeit an arbitrary determination, is about the minimum that we think should be deployed for the maintenance of the tide of young people who are absolutely crucial for the vigorous system for research.

The issue here is partly a philosophical one. It is maintained by some as an extreme position that the Government should not be in training, while others question how you adjust the amount of training grants vis-a-vis the total available resources. The main difficulty about trying to plan and defend training grants at any given level is that we are really talking about maintaining what is needed 5 or 10 years hence in science, and given the year-to-year budgeting of the Congress and the NIH, obviously this is extremely difficult.

Training in our view is absolutely crucial. I would guess that if we could not support training, we should not support research for very long. I think it is that integral. There is no doubt that we have to make short-term adjustments. We have to raise stipends this year, so there will be some downturn in the number of trainees that we can support on the budget that we have. There will probably be a minor, I hope a relatively small decrease, in the numbers of trainees during fiscal '80 and '81.

Now with respect to M.D.'s, that is a more complex question. First of all the curves that show a rise in Ph.D.'s versus M.D.'s have reached a level of stability, so that now the percentage of the total number of principal investigators who are M.D.'s is holding steady at a figure which, to be sure, is considerably less than it used to be. There are many reasons why this is true not all of which have to do with the difficulties of attracting M.D.'s per se into scientific inquiry as a way of life.

Clearly when we started out 25 years ago, there was less professionalism in research. It was much easier to be a part-time investigator. That opportunity has practically disappeared. A career choice has to be made, and for an M.D. there are more attractions, more distractions. It is not surprising that the total number has declined from the earlier ratio and that the total ratio has changed. Also science is moving much faster than it was two decades ago, and it is very difficult to combine both clinical and laboratory skills to a sufficient degree to compete in today's really tough world.

We need to continue to have M.D.'s in training. We need clinical investigators or we could never translate all of the laboratory activities into practical applications, and we would be in a system that wasn't complete.

The M.D./Ph.D. programs will probably be modestly expanded, but we have to examine a certain number of problems. One problem that has been called to our attention is that M.D.'s now graduating with Ph.D. training qualifications in science are gravely concerned that if they have to spend 3 years in a totally clinical program, they are going to lose their skills, and they won't be able to get on the train when they go to the station. Now this is a serious problem, which is compounded by the views of the subspecialty boards that fail to allow M.D.'s the opportunity to keep up their science or even to move from one institution to another during that total 3 year period. We are gathering information now, and are going to talk with the subspecialty boards and make them acquainted with the problem to see if we can adjust these situations.

Exactly what additional devices need to be employed to maintain the number of M.D.'s interested in a career in research are not certain. The Academy, which is supported by us each year to examine the needs for training in this country, has a study of clinical research underway; and we have some activities of our own.

I suppose the attraction, as is true for the Ph.D., depends to a great degree on the predictability of research support. At the present time if you are really good, you can almost certainly count on getting a grant from NIH and having a career in science as long as you stay good. But competitiveness is rising. It is getting more difficult to fund the number of grants that are the same percentage of approved grants that we see, and we don't expect that situation to be relieved very much in 1980 and 1981. However we plan to use all the devices we have available to try to maintain that opportunity at about the same level. All that will really depend on the total budget that the President allows us, which will be made public in about the second week in January.

Now let me ask the assembled group a question. Suppose we were only able to pay one out of five grants that came to NIH and went to your study sections. Do you think that would cause you an acute embarrassment or difficulties above and beyond what you see now?

Comment: I wouldn't see it as increasing the difficulty, though it may increase the pressure considerably. My own sense of the way grants are considered is that there are some truly outstanding applications at the top that are readily identifiable, probably less than 20 percent of the total grants. I think the community would suffer, but I don't think the study sections would suffer by having to fund only one out of five grants.

Dr. Fredrickson: Do you think the morale of the study section members would suffer?

Comment: Indeed that might happen. But I do not think it would be a workload problem.

Comment: I was on during the years of the impounded funds. The attitude of the members ranged from severe depression to extreme hostility -- "why am I wasting my time even coming here when only 10 percent of the work that I do has any prospect of being funded?" I think that there might be an element of that again. If people are spending a lot of time going through grants that are never going to be funded, why waste their time?

Comment: We had this experience in the American Heart Association, where we were faced with being able to fund only 18 percent of the total grants, and it really didn't have much affect on the morale of the study sections. But I am not sure that the same experience would carry over to NIH.

Dr. Fredrickson: I asked the question to get reactions and to encourage and urge you not to be depressed by any single year convolutions which we may be headed for. I am not trying to predict. We may be better off than we thought, but I think that we are in a state of transition. Biomedical scientists have probably never been healthier in the sense of opportunity. I think this is not false optimism. The possibilities are simply extraordinary, far beyond what they were 20 years ago, because many doors have been open. At the same time there is no question but that biomedical science in this country is leveling out, that just maintaining it against inflationary pressures is going to be a tough job.

We are going to have to adapt to the new reality. It had to come and what we have to do is with wisdom, and certainly with some optimism, conclude that we can find a way to maintain this extraordinary system.

Question: I was pleased to hear your comments about training, and I wondered if you could comment about the political aspect of the NIH budget today. Is it simply a matter of general austerity and are there specific aspects of the budget that are made for political reasons?

Dr. Fredrickson: The NIH budget is subject to an extraordinary array of political pressures at every juncture. Virtually every group with a particular cause, whether it be conservation or support for particular diseases or activities, has special interests.

Of course the largest single pressure of the NIH budget is the same as what exists in every other place -- inflation and the intent to balance the budget on the part of the Administration in the face of increasing defense expenditures. Since a modest fraction of the whole budget is in the so-called controllable as opposed to the noncontrollable area, there is more competition for the dollar.

The problem has been compounded in the recent years by the addition in the Congress of its own budget limits. For the first time this year, the Congress is really under a budget limit, and the Appropriation Committees cannot go as far as they want. Last year they were under the same constraints, but they broke constraints; this year they are probably not going to be allowed to do that.

Now these are the strengths. Congress is tired of disease mandates; they find it too difficult to make these judgments. They also want to seek a way to stabilize science. They believe in biomedical research. For the last 3 years especially, they have been trying to find formulas for maintaining the budgets against inflationary cuts at some level.

Last year we negotiated long and hard with them, and we came down on the House side at least in terms of the number of new and competing grants that could be funded. The whole Congressional appropriation rested solely on ROIs, and Congress really learned what ROIs mean. They know how many study sections there are. They know how much you work, how much you do for nothing. They are very well appraised of the peer review process and, in fact, they back it. They believe in it consummately.

This year we decided to initiate an attempt for the next 5 years to get them to make as reasonable a promise as they can ever make on a year-to-year basis for predictability of grant support. That request is in a research planning document that has not yet been released by the Department. I hope it comes out soon.

Now within health science there are, of course, enormous currents of competition. The regulatory agencies require us to develop certain programs to attempt to address certain needs and to keep science moving in a practical way. The requirements for measurement of new technology and the whole cost containment demand upon health science cannot be ignored. If we don't meet these demands, there won't be any reason, any impulse on the part of society to continue to support some small island of sanctuary against these social pressures.

We have to maintain this continuum knowing that the Congress and everybody else can't make decisions about the areas you deal with. You judge the grants. Mr. Kennedy wants to put laymen on your study sections; that won't destroy you, but they won't help you make the technical judgments you have to make. You have to make them down at this end of the continuum. We would like to make sure that the so-called science base activities are supported at a predictable level. We will trade that opportunity for a guarantee that we will continue to maintain the continuum in the direction of practical application, that we won't neglect the consequences of the inventions that arise out of discovery, that we will get them to the consumer. In doing that, of course, NIH, very strongly maintains certain boundaries around its activities. We maintain them much more strongly than we could 4 or 5 years ago, because I think we have shown that science cares about the practicality of what it is doing.

But the Congress and the Administration are struggling to make decisions. How can you wisely set aside a certain amount of public money for what is basically an investment in a distant future?

The social contract that maintains societal support of research is not a natural law. Not all societies find it within their interest to maintain very much of a margin for this kind of activity. America came aborning in a time at the end of the Enlightenment where this was just the thing to do. While it isn't in the Constitution, some people maintain it was an original intent of the Founding Fathers. However, there is nothing that guarantees an allocation of a particular portion of society's money for this kind of activity. Its justification has to come by a constant reiteration of the need, of the advantages, of the values of what has gone on before and, to me, a demonstration that we care. We care integrally about the quality of what we ask the public to buy, and that is where you come in.

Question: I wonder if any consideration has been given to getting money by formula. Most industries have set rules about investing so much of their capital in research development, and whether we like it or not, we tend to be arriving in this country at some degree of paid for medicine. Would it be a reasonable thing to say that a percentage of the national medical bill ought to go into research and development activities, and as the cost increases, this should reflect the need for more research and development?

Dr. Fredrickson: We do it all the time. Nobody knows what the right percentage should be or exactly what the best base would be, but the current favorite model is the health care costs.

Question: Do you use that when you go to Congress?

Dr. Fredrickson: We don't use it with Congress. We use it with the Administration. However, we are not allowed to propose to Congress our own solutions except when we may be asked. Nevertheless there is plenty of currency to that idea. It is just that nobody is willing to make a based formula kind of support for almost anything except, I guess, social security, which has to be protected.

Comment: My second suggestion is that we find a way to get a percentage of the overrun on the next B1 bomber or perhaps a battleship or something like that.

Dr. Fredrickson: No, but there is something much more practical that we can do. We spend between one and two hundred million dollars now on clinical trials, and there is going to be continuation of this activity. A much stronger and ultimately persuasive argument is that the fiduciary, who pays the health bill and who wants these questions answered for the sake of determining compensation rates, ought to pay the costs. As the health care financing agency knows, all we are out for is a reasonable share, even one percent of its budget, in order to finance these very costly trials. I think that in the next 4 or 5 years you are going to learn a lot about that, and probably there will be some adjustment so that we can get rid of that big burden in a perfectly honorable and quite justifiable way. But it has not yet been settled or agreed upon by any of the support people.

Question: Would you give me an overview of the new missions, the new roles of the next 5 to 10 years that you visualize for the National Institutes of Health?

Dr. Fredrickson: In the next few years we will probably be returning to many of our traditional roles rather than expanding into new areas. Four or 5 years ago when I came here, I thought that defining the nature of the boundaries of NIH and examining many of the new rules which it had just inherited or was inheriting from the Congress were important. I felt very strongly that the role of NIH was to examine what was wrong in the health system that science could correct, what the needs were that the Congress, the Administration and public saw with the application of medical science to the human condition, and then to try to adjust and address as many of those issues as was appropriate for this agency.

As a result we went into a number of activities, such as consensus searches, occupational health, concerns of the Food and Drug Administration and Environmental Protection Agency, toxicology, and determination of carcinogens. We urged the Secretary to develop, and took the initiative in putting together, a National Toxicology Program where for the first time the regulators and the researchers now sit down on a regular basis and together look at their needs.

In other words we were trying to get the cutting edge of science and the needs of society together. We looked at issues of health promotion, at the control matters that were mandated, and at the urgent need for dissemination of information about cancer in order to get the best treatment. We began to encourage the Public Health Service to add strength to some of its other agencies, such as the Center for Disease Control, to give it primarily as much health promotion clout as possible, because too much health promotion is in my view a threat to the objectivity of the scientific world message. It is like regulatory activity; you can't go near it, and we were being pulled towards regulation. We are still dragging near the edge with the DNA guidelines, which was an example of a real crisis of an anxious society concerned about possible successive powers of scientific techniques. We managed to keep that out of the statutory or rigid statutory mode into guidelines that I think are effective.

To make a long story short, we have been able to trim away a number of things that threatened NIH and ultimately its ability to be highly objective in science. The nation needs a sharp instrument for applying the scientific method to problems in the medical area. It must not be encumbered by subjective burdens. For example the National Center for Health Care Technology was recently created to do much of our consensus work, certainly to put the value judgments on technical judgments that we have made.

What will be the missions of the NIH? NIH will continue to have a very large mission in applying science to answering health care questions such as clinical trials. I think NIH must do that, for it is the best instrument through its constituencies for taking up these terribly difficult, expensive long-term randomized studies. We are going to be moving as much as we can towards the preventive mode, insisting upon ambulatory care in research. I am not sure what our relationship will be with institutions in maintaining their stability to carry out the teaching that requires science to go on in its midst, but this is going to be very important. I think that in the main we will still be the principal science agency in the Government for the health sciences, but we will be in a role that will be very contiguous and complementary to many other agencies where these health missions have to be carried out.

References

1. *Classification of Etiologic Agents on the Basis of Hazard*. (4th Edition, July 1974). U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Office of Biosafety, Atlanta, Georgia 30333.
2. *National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses* (October 1974). U.S. Department of Health, Education, and Welfare Publication No. (NIH) 75-790.
3. U.S. Department of Agriculture, Animal and Plant Health Inspection Service.

Appendix C

Section I-E-5 states that exempt from these Guidelines are "Other classes of recombinant DNA molecules, if the Director, NIH, with advice of the Recombinant DNA Advisory Committee, after appropriate notice and opportunity for public comment, finds that they do not present a significant risk to health or the environment. (See Section IV-E-1-b(1)-(d).) Certain classes are exempt as of publication of these Revised Guidelines. The list is in Appendix C."

Under exemption I-E-5 of these Revised Guidelines are those recombinant DNA molecules that are propagated and maintained in cells in tissue culture and that are derived entirely from non-viral components (that is, no component is derived from a eukaryotic virus).

Appendix D

As noted above at the beginning of Section III-A, certain HV1 and HV2 host-vector systems are assigned containment levels as specified in the subsections of Section III-A. Those so classified as of publication of these Revised Guidelines are listed below.

* HV1—Unmodified laboratory strains of *Saccharomyces cerevisiae*

* HV1—The following specified strains of *Neurospora crassa* which have been modified to prevent aerial dispersion: (1) inl (inositolless) strains 37102, 37401, 46316, 64001 and 89601.

(2) csp-1 strain UCLA37 and csp-2 strains FS 590, UCLA101 (these are conidial separation mutants).

(3) eas strain UCLA191 (an "easily wettable" mutant).

HV1—Asporogenic mutant derivatives of *B. subtilis*. These derivatives must not revert to sporeformers with a frequency greater than 10^{-7} ; data confirming this requirement must be presented to NIH for certification. The following plasmids are accepted as the vector components of certified *B. subtilis* HV1 systems: pUB110, pC194, pS194, pSA2100, pE194, pT127, pUB112, pC221, pC223.

* HV2—The following sterile strains of *Saccharomyces cerevisiae*, all of which have the ste-VC9 mutation, SHY1, SHY2, SHY3, and SHY4. The following plasmids are certified for use: Ylp1, YEp2, YEp4, Ylp5, YEp6, YRp7, YEp20, YEp21, YEp24, Ylp25, Ylp26, Ylp27, Ylp28, Ylp29, Ylp30, Ylp31,

Ylp32, and Ylp33. These plasmids can be considered EK2 vectors when propagated in 1776.

Appendix E

As noted in the subsections of Section IV-E-1-b(1) the Director, NIH, may take certain actions with regard to the Guidelines after public notice and RAC consideration.

Some of the actions taken to date include the following:

- The following experiment has been approved: The cloning in *B. subtilis*, under P2 conditions, of DNA derived from *Saccharomyces cerevisiae* using EK2 plasmid vectors provided that an HV1 *B. subtilis* host is used.

- Unmodified laboratory strains of *Neurospora crassa* can be used in all experiments for which HV1 *N. crassa* systems are approved provided that these are carried out at physical containment one level higher than required for HV1. However, if P3 containment is specified for HV1 *N. crassa*, this level is considered adequate for unmodified *N. crassa*. For P2 physical containment, special care must be exercised to prevent aerial dispersal of macroconidia, including the use of a biological safety cabinet.

- P2 physical containment shall be used for DNA recombinants produced between members of the genera *Streptomyces* and *Micromonospora* except for those species which are known to be pathogenic for man, animals or plants [2A].

- Cloned desired fragments from any non-prohibited source may be transferred into *Agrobacterium tumefaciens* containing a Ti plasmid (or derivatives thereof), using a nonconjugative *E. coli* plasmid vector coupled to a fragment of the Ti plasmid and/or the origin of replication of an *Agrobacterium* plasmid, under containment conditions one step higher than would be required for the desired DNA in HV1 systems (i.e. one step higher physical containment than that specified in the subsections of Section III-A). Transfer into plant parts or cells in culture would be permitted at the same containment level (one step higher).

- *Bacillus subtilis* strains that do not carry an asporogenic mutation can be used as hosts specifically for the cloning of DNA derived from *E. coli* K-12 and *Streptomyces coelicolor* using NIH-approved *Staphylococcus aureus* plasmids as vectors under P2 conditions.

- *Streptomyces coelicolor* can be used as a host for the cloning of DNA derived from *B. subtilis*, *E. coli* K-12, or from *S. aureus* vectors that have been approved for use in *B. subtilis* under P2 conditions.

Dated: November 26, 1979.

Donald S. Fredrickson,

Director, National Institutes of Health.

[FR Doc. 79-38841 Filed 11-29-79; 8:45 am]

BILLING CODE 4110-08-M

ACTION: Notice of proposed actions, under NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: This notice sets forth actions proposed by the Director, NIH, under the 1978 NIH Guidelines for Research Involving Recombinant DNA Molecules (43 FR 60108), and introduces the publication of proposed NIH Guidelines.

FOR FURTHER INFORMATION CONTACT: Additional information can be obtained from Dr. William J. Gartland, Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, Maryland 20205. (301) 496-6051.

SUPPLEMENTARY INFORMATION: I am today issuing for public comment proposed revised NIH Guidelines for Research Involving Recombinant DNA Molecules. This action is taken in accordance with Section IV-E-1-b(1) of the NIH Guidelines (43 FR 60126) which says, "The Director's proposed decision, at his discretion, may be published in the Federal Register for 30 days of comment before final action is taken." This announcement is both a "Decision Document" explaining the background and reasons for the proposed decision and an Environmental Impact Assessment. Immediately following this announcement there appears a copy of the proposed revised NIH Guidelines. Both the Decision Document/Environmental Impact Assessment and the proposed revised Guidelines are issued for public comment for a period of 30 days. Written comments and inquiries should be addressed to the Director, National Institutes of Health, Bethesda, Md. 20014. All comments received will be available for public inspection at the Director's office on weekdays (Federal holidays excepted) between the hours of 8:30 a.m. and 5 p.m. The structure of this Decision Document/Environmental Impact Assessment is as follows:

I. History of the NIH Guidelines Through 1978.

II. Revision of the December 1978 Guidelines.

III. The "E. coli K-12/P1 Recommendation" Made by the RAC at the September 6-7, 1979, Meeting.

IV. Other Recommendations Made on "Major Actions" by the RAC at the September 6-7, 1979, Meeting.

I. History of the NIH Guidelines Through 1978

The history leading to the issuance of original 1976 NIH Guidelines for Recombinant DNA Research is described in detail in the Environmental Impact Statement on the 1976 Guidelines, and in the "Decision Document" accompanying the

* These follow the assigned containment levels as specified in the subsections of Section III-A with one exception. This exception is that experiments involving complete genomes of eukaryotic viruses will require P3+HV1 or P2+HV2 rather than the levels given in the subsections of Section III-A.

Guidelines in the **Federal Register** of July 7, 1976. Key points in the history included:

- The Maxine Singer-Dieter Soll letter (*Science* 181, 1114, 1973) arising from the Gordon Research Conference on Nucleic Acids of July 1973.

- The Paul Berg et al. letter to *Science* (185, 303, 1974) calling for the NIH to establish an advisory committee to write guidelines.

- The Asilomar conference of February 1975.

- The work of the NIH Recombinant DNA Advisory Committee (RAC) through 1975, resulting in the proposed guidelines of December 1975.

- The special meeting of the Advisory Committee to the Director, NIH, on February 9-10, 1976, to review the proposed guidelines.

- Final issuance of the NIH Guidelines on June 23, 1976 (published in the **Federal Register** on July 7, 1976).

The history from the period July 1976 to December 1978 includes the following key points:

- Deliberations on revisions by the RAC during 1977, resulting in proposed revisions published for comment in the **Federal Register** on September 27, 1977 (42 FR 49596).

- A public hearing on the revisions, at the meeting of the Advisory Committee to the Director, NIH, December 15-16, 1977.

- Publication for public comment in the **Federal Register** on July 28, 1978 (43 FR 33042) of new proposed revised guidelines accompanied by a detailed Decision Document and a detailed Environmental Impact Assessment.

- A public hearing on the proposed revisions, chaired by the General Counsel of HEW, on September 15, 1978.

- Publication of revised guidelines on December 22, 1978 (43 FR 60080), accompanied by a detailed Decision Document and Environmental Impact Assessment.

The entire history is extensively documented in Volumes 1-4 of "Recombinant DNA Research"—a series constituting a readily available public record of activities in regard to the NIH Guidelines.

II. Revision of the December 1978 Guidelines

The December 1978 NIH Guidelines for Research Involving Recombinant DNA Molecules (43 FR 60108) include procedures for changing the Guidelines. As detailed in Section IV-E-1-b-(1) of the Guidelines, this involves consideration of the proposed changes by the NIH Recombinant DNA Advisory Committee (RAC) with an opportunity for public and Federal agency comment

and with publication in the **Federal Register** of the final decision by the Director, NIH.

On April 11, 1979, there appeared in the **Federal Register** (44 FR 21730) the first changes in the Guidelines under these new procedures. There, I published background information on recommendations made by the RAC at their February 16-17, 1979, meeting, and promulgated certain changes in the Guidelines.

In the **Federal Register** on July 20, 1979 (44 FR 42914), I published background information on recommendations made by the RAC at their May 21-23, 1979, meeting, and promulgated certain additional changes in the Guidelines.

At the most recent RAC meeting on September 6-7, 1979, additional changes in the Guidelines were recommended. Parts III and IV of this announcement give background information on these recommendations and my proposed decision on them. Immediately following this announcement, there appear proposed revised NIH Guidelines for Research Involving Recombinant DNA Molecules (which I will refer to as the November 1979 proposed Guidelines). These were obtained by incorporating into the December 1978 Guidelines all the changes made following the February 16-17, May 21-23, and September 6-7 RAC meetings.

III. The "E. coli K-12/P1 Recommendation" Made by the RAC at the September 6-7, 1979, Meeting

The organization of Part III of this announcement is as follows:

In Section III-A, the historical background of the "E. coli K-12/P1 Recommendation" is given. In summary, this was a recommendation that experiments involving propagation of recombinant DNA in EK1 hosts should be exempted from the Guidelines, but be carried out at the P1 level of physical containment, and be registered with the Institutional Biosafety Committee (IBC) without the requirement for IBC prior review.

Section III-B specifies a framework for analyzing how a hazardous situation might result from these changes in the Guidelines, and then shows the low probability of each of a series of steps required for a harmful effect—including escape of *E. coli* K-12 in significant numbers from a P1 laboratory, implantation and persistence of *E. coli* K-12 in the human intestinal tract, conversion of *E. coli* K-12 into an epidemic pathogen, and transmission of recombinant DNA to other organisms.

Section III-C gives my responses to issues raised in correspondence concerning the recommendation.

Section III-D discusses alternatives which I considered prior to my proposed decision.

Section III-E gives my proposed decision. In summary, these experiments are not to be exempted from the Guidelines. I proposed to accept the recommended containment level of P1 and EK1, and the requirement that these experiments be registered with and reviewed by the IBC. Prior review by the IBC would not be required before initiation of most experiments in this class. Prior review and approval by the IBC would be required, however, for experiments in which there is a deliberate attempt to have the *E. coli* K-12 efficiently express a gene coding for a eukaryotic protein. Registration of these experiments with NIH, and review of them by NIH, would not be required.

III-A. Background

Of all the recommendations arising from the last three meetings of the RAC, the one that has generated the greatest number of letters and the most discussion at the RAC meetings is a proposal adopted by the RAC on September 6, 1979, by a vote of 10 in favor, 4 opposed, and 1 abstention, that:

Those recombinant DNA molecules that are propagated in *E. coli* K-12 hosts not containing conjugation-proficient plasmids or generalized transducing phages, when lambda or lambdoid bacteriophages or non-conjugative plasmids are used as vectors, are exempted from the Guidelines, subject to the prohibitions of I-D-1 through I-D-6. Prior to initiation of the experiments, investigators wishing to carry out such experiments must submit a registration document that contains (a) a description of the source(s) of DNA, (b) nature of the inserted DNA sequences and (c) the hosts and vectors to be used. This registration document must be dated and signed by the investigator and filed only with the local IBC with no requirement for review by the IBC prior to initiation of experiments in these categories.

(In referring to this recommendation during my analysis below, I will call it the "E. coli K-12/P1 Recommendation.")

At my request, the NIH Office of Recombinant DNA Activities (ORDA) has prepared a 312-page book entitled "Background Documents on E. coli K-12/P1 Recommendation." This contains a history of the RAC consideration of this proposal at both its May 1979 and September 1979 meetings, and includes copies of all correspondence received and documents reviewed by the RAC at these meetings. This document: (i) is now available for public inspection at ORDA; (ii) can be made available (in whole or in part) to any requester upon payment of reproduction costs; and (iii) will be published (and subsequently may be purchased through the U.S.

Government Printing Office) as part of Volume 5 of "Recombinant DNA Research," a series constituting a public record of activities in regard to the NIH Guidelines.

I have carefully examined this extensive record in detail. A summary of the record is as follows:

1. A proposed exemption was published for public comment in the *Federal Register* on April 13, 1979, as follows:

Those recombinant DNA molecules that are propagated in *E. coli* K-12 hosts not containing conjugation-proficient plasmids or generalized transducing phages, when lambda or lambdoid bacteriophages or non-conjugative plasmids are used as vectors, are exempt from the Guidelines.

2. Dr. Wallace Rowe, a member of the RAC and one of the two proposers of the exemption, sent to the RAC members on May 4 a document supporting the exemption, including copies of a number of published scientific papers and letters from immunologists concerning their assessment of the possibility of autoimmune disease being caused in man as a result of recombinant DNA experimentation.

3. Also sent to the RAC members prior to their May 21-23 meeting were other documents commenting on risk-assessment in general and the Rowe-Martin polyoma experiments in particular, as well as four letters commenting directly on the proposed exemption: two supporting the proposal and two considering it premature.

4. At the May 21-23 meeting, the RAC discussed the proposed exemption for several hours. A motion was passed by a vote of 17 to 0, with 3 abstentions:

That the chair appoint a working group to: (a) conduct a rigorous scientific analysis of the *E. coli* K-12 host-vector systems with specific regard to the state of evidence of attendant biohazards of such studies/systems; (b) explore existing nonRAC (medical microbiology) mechanisms for regulating these specific host-vector systems; (c) develop proposals for "new" devices for ensuring laboratory safety standards with such systems; and (d) report the results of this working group to the full RAC for its consideration.

Later in the meeting, Dr. David Baltimore recommended that recombinant DNA experiments involving *E. coli* K-12 host-vector systems be permitted under P1 conditions, rather than be totally exempt from the Guidelines. He said that his proposal would involve registration with the local IBC with the forwarding of a registration document to ORDA. The RAC voted 18 to 3, with 1 abstention, in favor of recommending Dr. Baltimore's

proposal for consideration by the Working Group.

Later in the meeting, Dr. Jane Setlow, the RAC chairman, appointed Drs. Luther Williams (chairman), Susan Gottesman, Richard Novick, and Samuel Proctor to this "P1/EK1" Working Group.

5. The P1/EK1 Working Group deliberated and submitted the following proposal which was published for comment in the *Federal Register* on July 31, 1979:

Those recombinant DNA molecules that are propagated in *E. coli* K-12 hosts not containing conjugation-proficient plasmids or generalized transducing phages, when lambda or lambdoid bacteriophages or non-conjugative plasmids are used as vectors, can be handled at P1 and are exempted from the Guidelines.

6. Between the May and September RAC meetings, 14 letters commenting on the proposal were received and transmitted to the RAC members. All the commentators expressed strong support for the proposed exemption. Most of them supported the original proposal for complete exemption as published in the *Federal Register* on April 13, 1979. One of these letters was signed by 183 scientists who attended the 1979 Gordon Research Conferences on Nucleic Acids and on Biological Regulatory Mechanisms.

7. In addition to letters commenting directly on the *Federal Register* proposal, other relevant documents sent to the RAC prior to the September 6-7 meeting included an additional letter on the Rowe-Martin polyoma experiment, a background document from the P1/EK1 Working Group, and a manuscript on a framework for assessing the potential risks of recombinant DNA experiments prepared by Dr. Sidney Brenner for the United Kingdom Genetic Manipulation Advisory Group.

8. Distributed at the September 6-7 meeting were a summary of the major recommendations of an *ad hoc* National Institute of Allergy and Infectious Diseases working group on risk-assessment and a more detailed background document on *E. coli* K-12, prepared by the P1/EK1 Working Group.

9. At the September 6-7 meeting, several hours were spent discussing this proposal (I have reviewed a transcript of this portion of the meeting). Among the items covered during the discussion were: the interpretation of the Rowe-Martin polyoma experiments; the interpretation of two papers which appeared in the July 1979 edition of the *recombinant DNA Technical Bulletin*, "Testing of Host-Vector Systems in Mice" by Rolf Freter et al., and "Survival of *E. coli* Host-Vector systems

in the Human Intestinal Tract" by Stuart Levy and Bonnie Marshall; and the status of the NIH Risk Assessment Program. Questions discussed included: How likely is the escape of *E. coli* K-12 from the laboratory? What is the likelihood of its persistence? (survival without selective advantage?) What is the possibility of a reversion of its disabling properties?—or transfer of its DNA to a wild type strain? How likely and how dangerous would the colonization of humans by *E. coli* bacteria making a "foreign" protein be?—considering the danger either due directly to action of the "foreign" protein or due to induced autoimmunity? How much should the RAC consider imaginary hypothetical hazards and how much should it concentrate on perceived real hazards? How should one extrapolate from current data to set reasonable containment levels for experiments?

Concluding this discussion, the RAC voted 10 to 4, with 1 abstention, for the "*E. coli* K-12-P1 Recommendation."

Section III-B of this document analyzes in detail the issues discussed by the RAC prior to their voting on the "*E. coli* K-12/P1 Recommendation."

III-B. Analysis:

This section begins with a framework for analyzing how a hazardous situation might result from the recommended changes in the Guidelines, and then shows the low probability of each of a series of steps required for a harmful effect.

Framework for Analysis

As a framework for analyzing how recombinant DNA experimentation might lead to a hazardous situation, the following appeared in the NIH Environmental Impact Statement on the 1976 Guidelines, and remains valid today:

The hypothetical mechanisms by which insertion of foreign genes into cells or viruses might result in the formation of hazardous agents are . . . in principle, applicable to persons, animals, and plants. There is, as stated before, no known instance in which a hazardous agent has been created by recombinant DNA technology. Current knowledge permits no more than speculation that such agents may be produced and an equally speculative assessment of the nature and extent of hazards associated with a particular recombinant DNA experiment. . . .

In order that any potential hazard be realized, it is necessary that each of a number of sequential events occur. Each event in the sequence is possible only if the earlier events have occurred. The organism must—

- (a) Contain foreign genes, -
- (b) Escape from the experimental situation,
- (c) Survive after escape,

(d) Become established in an environment permitting its growth and multiplication.

(e) Contact other living organisms in a significant manner, including contact by a sufficient number of organisms to ensure survival and growth and to cause infection. Note that the environment in (d) may be a living organism itself.

In those cases where the detrimental effect would result from the formation of a harmful protein, the organism containing the recombinant DNA would have to—

(f) Contain a gene for a potentially harmful protein.

(g) Be able to express the foreign gene (that is, synthesize the corresponding protein) and

(h) Synthesize the protein in sufficient quantity to be deleterious to the infected organism.

The overall probability of a detrimental effect resulting from the formation of a harmful protein is then equal to the product obtained by multiplying together the probability of each event, (a) through (h).

In those cases where the foreign DNA itself might be the cause of undesirable effects, another set of events must be considered. Where the foreign DNA is presumed to increase the pathogenicity of the initial host cell or virus, the inserted DNA must—

(i) Impart a selective advantage for growth to the carrier of the recombinant DNA as compared with the original cell or virus.

(j) Alter the metabolism of the carrier so that it becomes disease-producing.

The overall probability of a detrimental effect by this mechanism is then equal to the product obtained by multiplying together the possibilities of events (a) through (e) times (i) through (j).

In the case where the foreign DNA is presumed to cause undesirable effects by virtue of its transfer out of the original recipient and reinsertion into cells of another species, the DNA must—

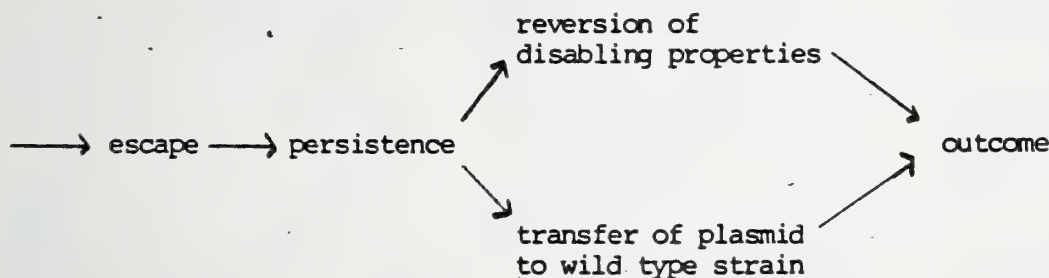
(k) Leave the original recipient without being destroyed.

(l) Survive transfer to another cell.

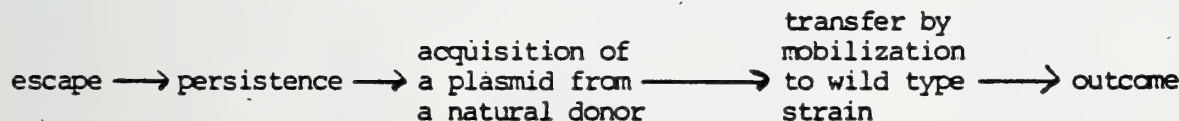
(m) Become associated with the other cell in a stable manner, either as an independent element or by natural recombination.

The overall probability of an undesirable effect arising by means of the secondary transfer mechanism is equal to the product obtained by multiplying together the probabilities of events (a) through (e) and (k) through (m).

A more recent framework for assessing the risks of recombinant DNA experiments was prepared by Dr. Sidney Brenner for the United Kingdom Genetic Manipulation Advisory Group. This document, which is part of the "Background Documents on *E. coli* K-12/P1 Recommendation" available from ORDA, was discussed by the RAC at their September, 1979, meeting. The Brenner document uses "generation trees." He gives examples such as:



or



As Dr. Brenner points out in a letter of July 26, "It is important to recognize that if any of the factors which are used can be assigned zero, then everything must be zero for that particular event. Thus if something does not express, that is enough; if it expresses and if the product has no biological target, that too is enough; and if it expresses and has a biological target and cannot gain access to it, that also is of no consequence."

Both frameworks (i.e., that of the EIS or of Brenner) lead to the conclusion that if any of the multiple steps leading to the final outcome has a zero probability, then the probability of the final outcome is zero. If no step has zero probability but if each sequential step leading to the final outcome has a low probability, then the final outcome has an exceedingly low probability.

What is the Likelihood of *E. coli* K-12 Escape From A P1 Laboratory?

For an organism containing recombinant DNA to cause a public

health hazard, it must first escape from the laboratory.

The NIH Guidelines specify in Section II-A that:

The first principle of containment is a strict adherence to good microbiological practices. Consequently, all personnel directly or indirectly involved in experiments on recombinant DNAs must receive adequate instruction. This shall as a minimum include instructions in aseptic techniques and in the biology of the organisms used in the experiments, so that the potential biohazards can be understood and appreciated.

The definition of P1 physical containment in addition requires the following:

"II-B-1-a-(1). Laboratory doors shall be kept closed while experiments are in progress.

II-B-1-a-(2). Work surfaces shall be decontaminated daily, and immediately following spills of organisms containing recombinant DNA molecules.

II-B-1-a-(3). All biological wastes shall be decontaminated before disposal. Other contaminated materials, such as glassware,

animal cages, and laboratory equipment, shall be decontaminated before washing, reuse, or disposal.

II-B-1-a-(4). Mechanical pipetting devices shall be used; pipetting by mouth is prohibited.

II-B-1-a-(5). Eating, drinking, smoking, and storage of foods are not permitted in the laboratory area in which recombinant DNA materials are handled.

II-B-1-a-(6). Persons shall wash their hands after handling organisms containing recombinant DNA molecules and when they leave the laboratory.

II-B-1-a-(7). Care shall be taken in the conduct of all procedures to minimize the creation of aerosols.

II-B-1-a-(8). Contaminated materials that are to be decontaminated at a site away from the laboratory shall be placed in a durable leak-proof container, which is closed before removal from the laboratory.

II-B-1-a-(9). An insect and rodent control program shall be instituted.

II-B-1-a-(10). The use of laboratory gowns, coats, or uniforms is discretionary with the laboratory supervisor.

II-B-1-a-(11). Use of the hypodermic needle and syringe shall be avoided when alternative methods are available.

II-B-1-a-(12). The laboratory shall be kept neat and clean.

Two requirements of P1 are most important. First, all biological wastes are to be decontaminated. *E. coli* are very sensitive to chemical disinfection. (*Disinfection, Sterilization and Preservation*, Seymour S. Black, editor, second edition, Lea and Febiger, 1977.) Second, mouth pipetting is prohibited. In the 1976 NIH Guidelines, mouth-pipetting was permitted at the P1 level. Mouth-pipetting was prohibited at the P1 level in the Guidelines promulgated in December 1978. The "Decision Document" accompanying proposed revised guidelines in the *Federal Register* on July 28, 1978, said:

A number of commentators have urged that mouth pipetting be prohibited at the P1 level of physical containment. This is strongly endorsed by NIH safety experts, who point out that this is an important safety feature, and that efficient new mechanical pipetting aids should not greatly hamper researchers. Also, the EMBO Standing Advisory Committee on Recombinant DNA Research "believes that mouth pipetting should be prohibited in P2-P4 laboratories." In addition, the Working Group of American virologists which met on April 6-7, 1978, to review the report of the U.S.-EMBO Workshop To Assess Risks for Recombinant Experiments Involving the Genomes of Animal, Plant, and Insect Viruses wrote the following in their report: "In its deliberations, the Working Group was impressed with the safeguards afforded by a ban on mouth pipetting for recombinant DNA experiments involving *E. coli* K-12 host-vectors. The group felt that the only plausible way *E. coli* K-12 could gain entry into laboratory workers was by oral ingestion. The analysis contained in the U.S.-EMBO Report was predicated on the remote possibility that *E. coli* K-12, containing eukaryotic viral DNA, would be swallowed and the viral DNA insert would be delivered to a tissue in the body which ordinarily would be inaccessible to the virus. A prohibition of mouth pipetting would clearly prevent this sequence of events from even beginning. The Working Group therefore, recommended that no mouth pipetting be allowed at any level of physical containment (including P1) when working with *E. coli* K-12."

The Environmental Impact Assessment accompanying proposed revised guidelines in the *Federal Register* on July 28, 1978, said:

A major change . . . is the banning of mouth pipetting at the P1 level, meaning that mouth pipetting is now banned for all experiments covered by the guidelines. Since the only plausible way *E. coli* K-12 could gain entry into laboratory workers is by oral ingestion, this ban greatly reduces the possibility that any organisms containing recombinant DNA will escape and thus minimizes the risk of environmental impact.

P1-type laboratories are used around the world for diagnostic microbiological

purposes, which involve handling many common pathogens. There is no evidence that the public has ever been endangered by the diagnostic and research efforts of the many private, city, county, and State microbiological laboratories associated with hospitals and public health departments. While accidental infections in laboratory workers have occurred, no epidemic or hazard to the public health has ever been shown to have arisen from work conducted in accordance with the basic safe practices required in a P1-type laboratory.

The main additional safety features of P2 and P3 as compared with P1 are the use of a biological safety cabinet, controlled air flow, and access control. These features are of primary importance in dealing with organisms transmitted by the respiratory route. For enteric organisms, such as *E. coli*, the main route of transmission is oral. Thus the ban on mouth pipetting, the requirement for decontamination, and observance of basic personal hygiene and sanitation practice, as required at the P1 physical containment level, are the essential safety features. The additional features of P2 and P3 provide additional safeguards against inhalation exposure, which is not a route of infection for *E. coli*.

What is The Probability of E. coli Causing An Epidemic By Person-to-Person Spread?

There are *E. coli* strains (other than *E. coli* K-12) which can cause disease in man. However, even for these, epidemic spread by person-to-person contact is extremely unlikely in adults. As summarized by Dr. Sherwood Gorbach (*Journal of Infectious Diseases* 137, 615, 1978):

The organisms are transmitted by the fecal-oral route. Person-to-person spread is rather unlikely, and for this reason secondary transmission of *E. coli* from the index case to another person is rarely observed. These epidemiologic characteristics are based on the requirement for a large oral inoculum of *E. coli* to initiate disease, an inoculum estimated to be at least 10^6 - 10^{10} organisms. Under natural circumstances, only highly contaminated sources such as food and water can serve as vehicles of transmission.

As discussed in an April 12, 1977, letter from Dr. Roy Curtiss (reprinted in the Environmental Impact Statement on the 1976 Guidelines):

In terms of communicability of *E. coli* K-12, we know that enteric diseases caused by enteropathogenic *E. coli* and various strains of Shigella, Salmonella and Vibrio are transmitted by contaminated food and water and that manifestation of disease symptoms requires consumption of approximately one

million bacteria. Such enteric diseases are seldom spread by aerosols . . . In terms of the more usual means for spread of enteric pathogens, it is evident that enteric diseases are very well controlled in the United States by sanitary engineering.

Certain strains of *E. coli*, such as those which produce enterotoxins, are responsible for a portion of acute diarrheal diseases of childhood and have been related to hospital nursery outbreaks of diarrheal disease. Data collected thus far suggest that *E. coli* diarrheal disease is relatively uncommon in the United States, but is more common in the developing world.

Dr. Eugene Gangarosa, writing in the *Journal of Infectious Diseases* 137, 634, 1978, concluded as follows:

Current evidence suggests that diarrheagenic *E. coli* are not important causes of disease in the sanitized urban centers of the United States at this time. However, enterotoxigenic *E. coli* are a leading cause of diarrhea among travelers who visit developing countries. The failure of diarrheagenic *E. coli* pathogens to gain a foothold in this country, despite problems with enteropathogenic *E. coli* in nurseries during the 1940's and 1950's and the more recent multiple introductions of enterotoxigenic *E. coli* by travelers returning from developing areas of the world, demonstrates the epidemiologic impotence of diarrheagenic *E. coli* in the relatively sanitized environment of the United States. Nondiarrheagenic *E. coli* seem to be major pathogens in community-acquired and nosocomial infections in extraintestinal sites.

In my judgment, the potential for an epidemic caused by the genetically manipulated K-12 strain of *E. coli* does not seem remotely possible. Even if disease could occur, it seems most unlikely that transmission from the laboratory to the community would take place, because of the reasons cited previously.

Is E. coli K-12 Pathogenic?

The "E. coli K-12/P1 Recommendation" mandates the use of *E. coli* K-12 hosts. Although there are pathogenic strains of *E. coli*, the enfeebled laboratory strain *E. coli* K-12 is not pathogenic. As noted in the Environmental Impact Assessment published in the *Federal Register* on July 28, 1978:

The laboratory variants of K-12 permitted in recombinant DNA experiments have never been reported cause disease, even in laboratory workers. K-12 has been grown in large quantities up to hundreds of liters containing as many as a trillion bacteria. These cultures have been produced in countless laboratories the world over, and under containment conditions lower than the minimal ones in the NIH guidelines.

As summarized by Dr. Sherwood Gorbach (*Journal of Infectious Diseases* 137, 615, 1978):

A critical constellation of virulence factors required by a microorganism in order to produce disease: (1) survival in the environment so that it can spread from animal to animal, (2) some mechanism for penetrating the skin or a mucosal surface such as the bowel, genitourinary tract, or oropharynx, (3) multiplication within the host, (4) systemic spread within the host, (5) resistance to host defense mechanisms, and (6) production of toxin or some other mechanism to damage the host to cause those symptoms associated with 'disease.' Freter has emphasized that the absence of any one of these characteristics will break the chain of events, rendering the microorganism avirulent . . . *E. coli* K-12 is intrinsically impaired in most, if not all, of these properties.

Can E. coli K-12 Be Made Pathogenic By The Insertion Of Recombinant DNA?

As discussed in the Environmental Impact Assessment which appeared in the *Federal Register* on July 28, 1978:

Seeking a consensus on the matter of risk assessment in recombinant DNA research, with particular reference to the use of *E. coli*, the National Institutes of Health sponsored a workshop in Falmouth, Mass., on June 20-21, 1977. In attendance were approximately 50 invited participants and observers, from the United States and abroad, including experts on all aspects of infectious disease. The following excerpt from a letter by the workshop chairman, Sherwood L. Gorbach, to Donald S. Fredrickson summarizes the principal conclusion: . . . "The participants arrived at unanimous agreement that *E. coli* K-12 cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts. On the basis of extensive studies already completed, it appears that *E. coli* K-12 does not implant in the intestinal tract of man. There is no evidence that non-transmissible plasmids can be spread from *E. coli* K-12 to other host bacteria within the gut. Finally, extensive studies in the laboratory to induce virulence in *E. coli* K-12 by insertion of known plasmids and chromosomal segments coding for virulence factors, using standard bacterial genetic techniques, have proven unsuccessful in producing a fully pathogenic strain. As a result of these discussions, it was believed that the proposed hazards concerning *E. coli* K-12 as an epidemic pathogen have been overstated. Such concerns are not compatible with the extensive scientific evidence that has already been accumulated, all of which provides assurance that *E. coli* K-12 is inherently enfeebled and not capable of pathogenic transformation by DNA insertions."

Does The Introduction Of Eukaryotic Shotgun DNA Into E. coli Alter Its Pathogenicity?

Numerous "shotgun" experiments have been performed, inserting pieces of eukaryotic DNA into *E. coli* K-12. In very few instances have the resulting recombinant-DNA-bearing bacteria

been specifically tested for pathogenicity. A paper sent to the RAC, and contained in "Background Documents on *E. coli* K-12/P1 Recommendation," reports on such a study by Drs. Hardy Chan, David Botstein, Wallace Rowe, and Malcolm Martin.

Shotgun DNA from *Saccharomyces cerevisiae* ligated into the plasmid pMB9 was inserted into *E. coli* K-12. Weanling mice were injected intracerebrally and intraperitoneally with the recombinant-DNA-containing *E. coli* K-12. Mice were sacrificed, the brains cultured in broth, and the broth culture injected into another group of mice, for five serial passages. The results showed that "Shotgun cloning of the majority of the genome of *Saccharomyces* into *E. coli* K-12 did not yield any clone with increased virulence for mice or with increased ability to adapt to mouse virulence as compared with K-12 carrying a non-recombinant plasmid."

Does E. coli K-12 Implant in the Intestinal Tract Of Laboratory Animals?

As summarized by Dr. Sherwood Gorbach (*Journal of Infectious Disease* 137, 615, 1978):

A number of investigators have tried in vain to implant *E. coli* K-12 in the intestinal tract of laboratory animals. Negative results have been noted in mice, rats, chickens, pigs, and calves. *E. coli* K-12 has been able to colonize the stomach of starved sheep.

Dr. Rolf Freter (*Journal of Infectious Diseases* 137, 624, 1978) reported that chi-1666 (an *E. coli* K-12 strain) "persisted beyond seven days in only one of a total of 144 conventional mice fed this bacterium." However, when the *E. coli* K-12 were first implanted in "germ-free" mice which were "conventionalized" later, "the strains established themselves in the indigenous flora for the length of the experiments (up to 85 days) at population levels normally assumed by *E. coli* in the conventional mouse."

Does E. coli K-12 Implant in the Human Intestine?

As noted in the Environmental Impact Statement on the 1976 Guidelines:

Experiments have shown that even after normal humans have ingested up to 10,000,000,000 K-12 cells, only transient multiplications of the bacteria in the intestines can be observed, and that after a time no K-12 can be detected in the feces. Thus, K-12 does not establish itself as a permanent resident of normal human beings.

It might be pointed out that animals, including humans, ingest large numbers of bacteria of many species daily. Most of these do not take up long-term residency. For example, a normal portion of yogurt may contain ten billion cells of the bacteria

Lactobacillus vulgaris; in spite of daily consumption, the *Lactobacillus* quickly disappears from the human bowel.

As summarized by Dr. Sherwood Gorbach (*Journal of Infectious Disease* 137, 615, 1978):

Since colonization of the intestine is felt to be an initial event in many pathologic states involving *E. coli*, it is natural that this feature has been the subject of several investigations. It is fair to state that there have been no instances in which the ingested strain of *E. coli* K-12 has been implanted in the human intestine. Smith fed eight different *E. coli* K-12 strains, containing various transmissible plasmids, to a volunteer at high doses (10⁹). Some strains could not be isolated at all from the feces, while others persisted in progressively reduced counts for a period of up to four days. The experiment was subsequently repeated, and there was again no persistence beyond four days. To increase the likelihood of implanting *E. coli* K-12 in the gut, Smith then used a K-12 strain that had inserted in it the colicin V (ColV) plasmid of a wild-type *E. coli* (ColV promotes the survival of wild-type *E. coli* in the intestinal tract.) When a volunteer consumed the K-12 strains with and without the ColV plasmid, the strains were eliminated from the feces in an equal time frame, none persisting more than four days.

Anderson attempted similar implantations with *E. coli* K-12 strains in eight volunteers who received doses of up to 10¹⁰ organisms. The maximal period of fecal excretion of the test strains was six days, with a mean of three days. These studies were repeated, again using eight volunteers, and the same findings were observed. Gorbach reported at this meeting unsuccessful attempts at implanting *E. coli* K-12 in two patients with defective bacterial clearing mechanisms in the small bowel. In one case, the patient has a stricture in the ileum, and the other patient had severe diarrhea due to cholera. The K-12 strain was eliminated from the small bowel and faeces within 24 hours in both patients.

Does E. coli K-12 Infect Laboratory Personnel?

A study of non-recombinant DNA workers in a laboratory studying *E. coli* K-12 and transmission-proficient R-plasmids (V. Petrocheilou and M. H. Richmond, *Gene* 2, 323, 1977) concluded that:

Faeces of laboratory workers who handled nalidixic acid-resistant *Escherichia coli* K-12 and R plasmids with multiple drug resistance markers were monitored every 2 or 3 days for over a 2-year period. Neither the K-12 bacteria nor any of these plasmids were ever found in the faeces. Since these R-plasmids are transmission-proficient and the work was carried out without any special precautions, one may conclude that there is not likely to be any practical risk for transmission of recombinant DNA when cloned in currently used transmission-deficient plasmids of *E. coli* K-12. . . . It is important to realize that studies carried out in this way give an overall view of the probability that a laboratory

strain will either itself become established in the gut or lead to the persistence of an R-plasmid in another *E. coli* line following plasmid transfer.

As such, it is therefore a composite measure of two separate processes: the probability of infection by the organisms under the conditions in which the laboratory work is carried out; and the ability of the organism, or its plasmid, to survive as a component of the faecal flora of the worker concerned. Although it could be argued that such a study is difficult to interpret because of its complexity, nevertheless the overall probability with which the process occurs is important in assessing the hazards of laboratory work with *E. coli* strains carrying R-plasmids. The results reported here suggest that *E. coli* K-12 lines, whether or not R-plasmids are carried, are unlikely to establish themselves as major components of the bacterial faecal flora of the workers handling the plasmids; and such a view is certainly consistent with the behaviour of *E. coli* K-12 strains carrying R-plasmids when deliberate attempts are made to establish them in the human gut by feeding them to volunteers (Anderson, 1975; Williams-Smith, 1975).

In the context of genetic manipulation experiments, these results suggest that some measure of safety attaches to the use of *E. coli* K-12 strains even in comparison to what might be expected for more commonly encountered smooth strains of *E. coli*. The margin of safety is increased very substantially when disabled versions of *E. coli* K-12, and/or plasmids that are not self-transmissible are used for in vitro recombination experiments.

An update of these data, sent to the RAC and contained in "Background Documents on *E. coli* K-12/P1 Recommendation," is the report "Summary of Conclusions from Feeding and Monitoring Experiments" by M. Richmond, as presented to the Risk-Assessment Subcommittee of COGENE on March 30, 1979. He notes, "Over a period of 26 months in Bristol; 12 months in London and 12 months in Seattle involving 64 subjects, there was no evidence that laboratory workers, or members of their families, acquired either bacterial strains or plasmids that were employed in the laboratory. This was true even in a few individuals working in the laboratory who received short courses of antibiotic therapy or, in one case, an individual who was on prophylactic antibiotic therapy."

Will E. coli K-12 Carrying Recombinant DNA Survive?

The Environmental Impact Assessment of July 28, 1978, said:

There are various indications that both host bacteria and plasmid or virus vectors containing inserted foreign DNA are less likely to survive and multiply than are the original organisms, except for the very unusual instances where the foreign DNA supplies some function, such as antibiotic resistance, that favors the organism in a

particular, non-natural environment. Natural selection results in the survival of only well-balanced and efficient organisms; unneeded genetic material tends to be lost. Essential functions are carefully controlled and are switched on and off as needed.

The activity of a particular gene product depends upon, and in turn influences, many other functions of a cell. Such uncontrolled, nonessential properties as might be introduced by foreign genes would probably not result in any advantage to the survival and multiplication of an otherwise well-balanced organism. Rather, the new properties might be expected to confer some relative disability. It is unlikely that elimination of a gene product by insertion of a foreign DNA sequence would be advantageous. More likely than not, any new properties derived from insertion of foreign DNA would confer some relative disability on the recipient organism. Therefore, it is probable that bacterial cells, plasmids, or viruses containing inserted foreign DNA would multiply more slowly in nature than the same cells or vectors without foreign DNA; and in a natural competitive environment, those organisms containing recombinant DNA would generally be expected to disappear.

New data relevant to this issue, sent to the RAC and contained in the "Background Documents on *E. coli* K-12/P1 Recommendation," were supplied by Dr. Donald Brown of the Carnegie Institution of Washington. *E. coli* K-12 containing no recombinant DNA were mixed with *E. coli* K-12 containing a number of different inserts (DNA from *Xenopus laevis*, *Drosophila melanogaster*, or *Bombyx mori*). In each case the *E. coli* K-12 containing no recombinant DNA outgrew the *E. coli* K-12 containing recombinant DNA.

Recent data sent to the RAC and contained in the "Background Documents on *E. coli* K-12/P1 Recommendation" supplied by Dr. Paul Burnett of Lilly Research Laboratories on May 8, 1979, indicated that when *E. coli* K-12 carrying recombinant plasmids containing insulin gene sequences were fed to conventional rats or mice, "the strain and plasmid are lost very rapidly."

Will Recombinant DNA Be Transmitted from E. coli K-12 to Other Organisms?

As described in the Environmental Impact Assessment (Federal Register July 28, 1978):

While it would appear impossible to render *E. coli* K-12 pathogenic by the introduction of foreign DNA, there is still to be considered whether the inserted fragment could be transmitted to another bacterium with which the K-12 comes in contact, including other strains of *E. coli*. Such a transmission might convert the recipient into a pathogen or render a pathogen more viable. The case of plasmid vectors is considered first.

Plasmids are intracellular particles composed of DNA and not dependent on chromosomes for their replication. Hence, they can be used as vectors, or vehicles for transporting foreign DNA into the bacterial host, where they multiply and propagate the genes they bear. Certain plasmids (called "conjugative") are inherently able to migrate from one bacterial cell to another. These are prohibited for nearly all recombinant DNA experiments. Only plasmids not capable or barely capable of spontaneous intercellular migration ("nonconjugative") may be used.

As summarized by Dr. Sherwood Gorbach (*Journal of Infectious Diseases* 137, 615, 1978):

Smith (1978) fed 10^9 *E. coli* K-12 organisms to a normal volunteer. He used several strains which contained self-transmissible plasmids of the F, I, or A2 transfer groups. These strains could transfer in vitro the tetracycline resistance plasmids to an *E. coli* K-12 recipient and to resident *E. coli* from the normal flora of the volunteer. When the strains were fed to the volunteer, however, they were eliminated from the feces within four days, and there was no evidence of in vivo plasmid transfer to resident strains or to susceptible K-12 and H123 *E. coli* strains fed in the same ingested sample. This experiment was repeated, and again there was failure to transfer in vivo the tetracycline resistance plasmid.

Anderson (1978) fed large number of *E. coli* K-12 organisms which contained a nonconjugative plasmid to eight volunteers. In no instance was plasmid transfer to normal flora demonstrated in vivo. However, in vitro studies showed that *E. coli* strains from the normal flora of three of eight subjects carried transfer plasmids which could mobilize one of the nontransmissible plasmids, but not the other. Anderson suggested that "transfer would therefore be possible if a suitable conjugative plasmid entered a strain carrying a nonautotransferring hybrid plasmid."

Curtiss (1978) described in vitro transfer experiments in which he measured the mobilization of a series of recently developed, nonconjugative plasmids under optimal laboratory conditions. He estimated that the maximal probability for transmission of such plasmid vectors from an *E. coli* K-12 host is 10^{-16} per surviving bacteria per day in the intestinal tract of warm-blooded animals. He emphasized that the chance of transfer is even less since other factors, not taken into account, would reduce transfer in the intestinal tract. The in vivo deterrents included the following factors. (1) Diminished bacterial metabolic activity leads to decreased conjugation. In the test tube, the generation time of *E. coli* is 20-40 min, but it is 4-6 hr. in the intestinal tract. (2) Conjugation is inhibited by fatty acids, bile, and other constituents of the gut. (3) Conjugation is inefficient at the pH and Eh (oxidation-reduction potential) of the intestine.

A study by Dr. Dean Hamer (*Science* 196, 220, 1977) looking at the ability of conjugative sex factors to mobilize nonconjugative plasmids with or

without inserted recombinant DNA concluded that "the insertion of foreign DNA into a plasmid had little effect on its mobilizability."

A recent study (1979) included in the "Background Documents on *E. coli* K-12/P1 Recommendation" is the paper "Survival of *E. coli* Host-Vector Systems in the Mammalian Intestinal Tract" by Drs. Stuart B. Levy, Bonnie Marshall, Andrew Onderdonk, and Debra Rowse-Eagle, which concludes, "These results demonstrated an absence of detectable transfer of pBR322 during transit in the intestinal tract of the human volunteers, despite survival of the laboratory K-12 strain of almost a week at reasonably high titers."

The Rowe-Martin polyoma experiments (copies of the published scientific papers are included in the "Background Documents on *E. coli* K-12/P1 Recommendation") provide valuable data on the question of the likelihood of an animal virus recombinant DNA insert being transferred out of an *E. coli* K-12 host cell used in its propagation into a eukaryotic cell.

What is the Probability of Recombinant DNA Experimentation Leading to Autoimmune Disease?

Included in the "Background Documents on *E. coli* K-12/P1 Recommendation" are copies of a letter sent by Dr. Wallace Rowe to leading immunologists and their replies. Appended to the Rowe letter were (1) a paper by Dr. Jonathan King (*Journal of Infectious Diseases* 137, 663, 1978) which says, "Several kinds of pathologies might result from infection by chimeric *E. coli* strains displaying foreign proteins. One model is an autoimmune condition associated with exposure to antigens cross-reacting with human antigens" and (2) a letter from Dr. Jon Beckwith which says "Several laboratories * * * have used recombinant DNA techniques to construct strains which produce hybrid proteins between the peptide hormones insulin and/or somatostatin and bacterial proteins * * * [There is] a real possibility that these modified peptide hormones could break tolerance/induce an autoimmune response in humans to their own hormones if they reached the appropriate sites in the body. This, in turn, could clearly have severe effects on the health of the affected individuals."

Dr. Rowe asked in his letter for an "objective evaluation of the evidence for or against the possibility of such disease mechanisms occurring." The responses received are included in the "Background documents on *E. coli* K-

12/P1 Recommendation." The respondents were Drs. Baruj Benacerraf, Norman Talal, Frank Dixon, Philip Paterson, William Paul, and Richard Asofsky. In summary, they concluded that the probability of recombinant DNA experimentation leading to autoimmune disease was remote,—"grossly exaggerated and based upon the occurrence of hypothetical events"—[One must distinguish] "between autorecognition (which is physiologic and necessary for proper immunologic communication), autoimmunity, and autoimmune disease."—"I see the eukaryotic proteins secreted by *E. coli* bearing foreign DNA sequences as no more likely to induce autoreactive immune responses than the negative antigenic constituents of this prokaryotic vector cell itself."

Ad Hoc working Group on Risk Assessment

An Ad Hoc working Group on Risk Assessment convened by the National Institute of Allergy and Infectious diseases met on August 30, 1979. They discussed the NIH Plan For A Program to Assess the Risks of Recombinant DNA Research which was published in the *Federal Register* on September 13 [44 FR 53410]. Specific areas of concern involving *E. coli* K-12 were discussed in detail; old evidence as well as evidence accumulated in the preceding months were reviewed. The Working Group expressed their "solid support for the proposed exemption of K-12 based cloning from the Guidelines providing that P1 laboratory practices were employed." This was reported to the RAC at their September meeting, and is contained in the "Background documents on *E. coli* K-12/P1 Recommendation."

Lack of Demonstrated Hazard To Date

The Environmental Impact Assessment of July 1978 stated, "No evidence has come to light that any of the thousands of individual recombinant DNA clones constructed over the last 5 years have yielded a product harmful to man or the environment. On the other hand, many examples of useful knowledge obtained through such techniques continue to accumulate rapidly." The negative aspect of this statement remains unchanged as of this date. The useful new knowledge obtained through the use of the technology has continued to accrue.

III-C. *Letters Received Subsequent to the September 6-7 RAC Meeting:* The "*E. coli* K-12/P1 Recommendation" made by the RAC on September 6 was reported in the press. Subsequently, I received 26 letters concerning this

recommendation. These letters are part of the book, "Background Documents on *E. coli* K-12/P1 recommendation," available from ORDA. The major points made in the letters, and my response to them, are as follows:

Only 10 of 25 Members of the RAC Voted in Favor of the "E. coli K-12/P1 Recommendation"

A number of commentators objected to the fact that only 15 RAC members voted on this issue, out of a total of 25 authorized members on the RAC. Since only 10 of these 15 voted in favor of the motion, they constituted less than a simple majority of authorized RAC members.

Although the RAC is authorized to have 25 members, at the September 6-7 meeting only 24 members were actually appointed. Three members missed the entire meeting. Ten attended only part of the meeting. Only eleven attended the entire meeting. Of these, one is the chairman, Dr. Setlow, who only votes in case of a tie.

HEW regulations (45 CFR 11.5) implementing the Federal Advisory Committee Act, applicable to all HEW advisory committees, state, "Unless otherwise established in the charter of the committee, a quorum shall consist of a majority of the committee's authorized membership." The charter of the RAC is silent on the matter of a quorum. The authorized RAC membership is 25; therefore, 13 RAC members constitute a quorum.

At the May 21-23, 1979, RAC meeting, a Working Group on Procedures was established. The Working Group reported at the September 6-7 RAC meeting. (A discussion of this item was originally scheduled as one of the first agenda items, but was moved to later in the meeting because the arrival of Dr. Ahmed, a member of the Working Group, was delayed.) The Working Group report had been sent to RAC members in advance of the September 6-7 meeting. It contained a number of recommendations on six issues: speaking time for members of the public; outside consultants; conflict of interest; working groups and subcommittees; presentation of agenda materials to the RAC; and quorum and voting procedures. Each of the recommendations was voted on at the September 6-7 meeting. Dr. Ahmed presented a minority view of the Working Group that "For major actions under the Guidelines, a quorum should consist of two-thirds of the committee membership (17 members)." After discussion of this proposal by the RAC, a substitute motion—that there be no change from current procedures for

major actions (i.e., that a quorum be 13)—was passed by the RAC with 10 in favor, 6 opposed, and 2 abstentions.

The RAC Was Not Adequately Prepared To Vote on This Issue

One new member of the RAC felt there may have been inadequate preparation "for taking action on this most important issue" and that "important recommendation may be made with inadequate discussion."

The large quantity of background material supplied to RAC members relevant to this and many other issues is burdensome. Even with diligent preparation, a member just joining the RAC will find the subject matter to be extremely complex. In reviewing the record, however, I am impressed with the many hours the RAC spent discussing this proposal during its last two meetings, and I believe that members in attendance at both did not lack time to air their views. Moreover, the preparation of the RAC for addressing this proposal included assignment of the question to a subgroup of its members for consideration between the May and September meetings.

The RAC is a unique type of NIH committee. The usual NIH public advisory committee system is "two-tiered." At the first level, technical experts are assembled on initial review groups (study sections), where judgments are made on the quality of scientific hypotheses and the likelihood that they can be tested by experimentation. At the second level, in separate committees, typically represented by the Institute Advisory Councils, a broader array of talents (lay as well as scientific) is assembled to advise on the relevance of the proposed research to NIH programs and on other matters of broad public interest. Until December 1978, advice to NIH involving recombinant DNA research essentially followed this two-tiered model. The RAC served primarily as an initial review group providing the NIH Director with advice on technical issues in recombinant DNA research. Only two of its sixteen members were laymen. For the second level review, I used the Advisory Committee to the Director, NIH. In preparing the original 1976 NIH Guidelines for Recombinant DNA Research and in drafting the 1978 revisions, the Director's Advisory Committee members provided the broader public perspective.

This was changed in a major revision of the Guidelines in December 1978. The membership of the RAC was expanded to include more scientific disciplines and more lay members. The usual dual

review was compressed into a single enlarged committee.

Procedures were also changed to assure opportunity for prior public comment on issues considered by the RAC. In this way, both the RAC and the NIH Director receive the benefit of such opinions in the deliberation of the proposals for continuing revision of the Guidelines.

These changes were made to safeguard two vital public interests in the use of these remarkable techniques. The first interest is safety. The second interest is access to the benefits of the technology. The operations of the RAC determine the proper balance of these interests.

I have admiration for the performance of the RAC. The pressures upon its members are great from all sides. They have not been stampeded, and they have not allowed the vital stream of decisions they must continuously provide to be obstructed. I have been impressed with the care that the RAC chairman, Dr. Jane Setlow, has taken to allow all points of view to be aired at the RAC meetings, and to continue discussion on each issue until all members have had opportunity to ask all the questions and make all the points they wished.

Prepare an Environmental Impact Statement

A number of commentators requested that NIH prepare an environmental impact statement on "the proposed exemption."

As discussed in Section III-E below, I am not proposing an exemption for these experiments. An environmental impact assessment is contained in this document relative to the actions I am taking.

NIH prepared an environmental impact statement on the original 1976 NIH Guidelines for Recombinant DNA Research. In the *Federal Register* on July 28, 1978, a proposed revision of the NIH Guidelines was published for public comment along with an environmental impact assessment. The revised Guidelines published in the *Federal Register* on December 22, 1978, were again accompanied by an environmental impact assessment. In that document (43 FR 60101), I explained in detail why I concluded that an environmental impact assessment rather than an environmental impact statement fully satisfied the requirements of the National Environmental Policy Act of 1969 (NEPA).

The original environmental impact statement on the 1976 Guidelines (137 pages plus extensive appendices) and the environmental impact assessments

published in the *Federal Register* on July 28, 1978 (182 *Federal Register* pages) and on December 22, 1978, contain extensive discussions on recombinant DNA, physical and biological containment, *E. coli* K-12, and the NIH Guidelines. Much of what was written there is still highly relevant. These earlier environmental impact statements/assessments, together with the environmental impact assessment contained in this document, in our judgment, fully satisfy NEPA.

Approve the "Exemption"

A number of commentators endorsed the exemption of all recombinant DNA experiments in *E. coli* K-12. (These letters were received after the September 6-7 meeting; many such letters were received earlier.) One commentator reported on results in his laboratory indicating that recombinant DNA is spontaneously lost from *E. coli* K-12 and that insertion of foreign DNA into bacteriophage lambda decreases its growth potential. He said, "Considering the loss of recombinant DNA from these micro-organisms during ideal growth conditions and considering the general lack of competition with wild type cells, I cannot conceive that *E. coli* K-12 containing recombinant DNA could find an ecological niche outside of the laboratory."

For a discussion of my proposed decision not to exempt all *E. coli* K-12 experiments, see Section III-E below.

Delay Any Change in the NIH Guidelines Pending Many More Risk-Assessment Experiments

One commentator wrote, "Any relaxation of the NIH guidelines for recombinant DNA research would appear to be quite unjustified, since the surface has barely been scratched with regard to risk-assessment studies." A second commentator wrote, "This important decision was also premature in terms of the present risk assessment studies being carried out by NIH contractors."

The original guidelines were constructed to minimize the effects if certain imaginable risks should arise from recombinant DNA experiments. A continuing reassessment of the probabilities that such risks exist is a necessity. Society expects and deserves a running balance between the benefits of using the recombinant DNA techniques and their possible harm. When certain requirements of the guidelines can no longer be justified, they should be changed. The guidelines limit and make considerably more expensive and difficult the use of recombinant DNA techniques that

would be the case without them. In the end unrealistic restriction will frustrate the general maintenance of necessary and reasonable precautions.

NIH is committed to continuing risk assessment using both special experiments and continuing synthesis of all the accumulated data. Some studies are specifically designed to answer questions about containment, survival, and behavior of "recombinant" organisms. Data are also supplied by careful analysis of the steady stream of information emerging from other recombinant DNA experiments, as well as new knowledge in the areas of microbiology, infectious disease, cell biology, and genetics. Preceding sections of this document describe old and new information and analyses bearing directly on the "*E. coli* K-12/P1 Recommendation." None of the specific risk-assessment studies now being carried out by NIH contractors is designed to yield information that will bear unequivocally on this decision. See further discussion on this point in Section III-D below.

Data Are Not Sufficient to Justify Exemption

Some commentators gave specific reasons for not exempting *E. coli* K-12 experiments from the Guidelines at this time. Some noted that there are conflicting interpretations of the significance of the Rowe-Martin polyoma risk-assessment experiments. Some cited specific additional risk-assessment experiments which they feel should first be completed. One commentator noted that much risk assessment data has been obtained using EK2 systems and said that these data should not be extrapolated to EK1 systems. In addition, he noted that certain data were used previously to justify the containment levels set in the December 1978 Guidelines and said, "One can thus ask what is the basis for the current committee's recommendation to use these same data to justify an additional lowering of containment?"

In response to the last point, I note that various new data, available first in 1979, were considered by the RAC along with "old" data. It is a continuous charge to the RAC to examine new data, but also to reexamine old data in coming to their recommendations.

In regard to the Rowe-Martin experiments, the results are published, the data available to all to analyze. A number of letters on this issue are included in the book "Background Documents on *E. coli* K-12/P1 Recommendation." At each of the last two RAC meetings, conflicting

interpretations on the experiments were openly discussed. Also discussed by the RAC was extrapolation of data obtained with EK2 systems to EK1 systems, and the perceived need for certain additional risk-assessment experiments to be completed. These are questions on which people will have different opinions. Indeed, in my analysis of the RAC discussion on this issue, I find these to be the major points which seemed to lead to the split vote by the RAC. That is it appears that the four RAC members who voted against the "*E. coli* K-12/P1 Recommendation" felt that certain additional risk-assessment experiments should be done first, including some experiments previously done with EK2 systems which they would like repeated with EK1. On the other hand, the 10 RAC members who voted in favor of the proposal judged that the data in hand were sufficient to justify the proposal.

Strong Directive to IBCs

One RAC member wrote:

I still have reservations about the exemptions and feel that if the proposal is accepted by Dr. Fredrickson, then a fairly strong directive to the IBC's is a minimum necessity * * * to the effect that they are expected to review the registration-MUA's at their earliest convenience, paying special attention to two questions: (1) is the experiment actually exempt and (2) does it involve the cloning of genes determining potentially hazardous polypeptides or other products. In the latter case, it might be suggested that a test of this possibility be performed. In the event of an irreconcilable difference of opinion involving the IBC and an investigator, ORDA should be consulted.

I agree with the recommendation for a strong directive, and have taken steps to ensure, when the final decision is made on the "*E. coli* K-12/P1 Recommendation," that not only Institutional Biosafety Committees but also institutional leaders will be informed of their special responsibilities with regard to these experiments.

Don't Exempt

A number of commentators urged that the experiments falling under the "*E. coli* K-12/P1 Recommendation" not be exempted from the Guidelines.—"I feel it is premature to exempt the vast majority of recombinant DNA experiments with *E. coli* K-12."—"I oppose the proposed exemptions of the Recombinant DNA Advisory Committee."—"The purpose of this letter is to urge against the approval of the proposed complete exemption of cloning *E. coli* K-12 hosts from the NIH recombinant DNA guidelines and to encourage a more moderate relaxation

of existing constraints as an alternate action."

As I discuss in Section III-E below, my proposed decision is not to approve an exemption for these experiments; they would be retained under the control of the Guidelines, including the requirement for P1 and EK1 containment.

III-D. Alternatives

In Section III-E of this announcement I provide a full exposition of my proposed decision on the "*E. coli* K-12/P1 Recommendation." A summary of this proposed decision was provided at the beginning of Section III. Before coming to this proposed decision, I considered a number of alternative actions which are discussed below.

Make No Change In The Guidelines Until Many More Risk-Assessment Experiments Are Completed

Some argued that no changes should be made in the Guidelines until many more risk-assessment experiments are completed.

I have discussed this in Section III-C above. NIH is firmly committed to an ongoing program of risk-assessment studies. It is responsible, however, for husbanding the resources for what are often very expensive and time-consuming studies. The experiments that are undertaken should seek to solve critical and, if possible, generic questions. We must be convinced that no significant risk to the worker or the public is inherent in the permissible work. Extrapolation from specific risk-assessment experiments to generic conclusions is always limited. Results in the mouse may not hold in man, or in all men; observations with one plasmid cannot be extended to all plasmids. The almost limitless permutations of possible transplanted genetic material, vectors and hosts, and of experimental conditions, means that few absolute answers can ever be obtained. Thus we cannot by any finite number of risk-assessment experiments, assign precise numerical probabilities to those risks judged extremely unlikely; and we can never consider the low probabilities to be zero under every conceivable condition. Nature has, by far, the longest string of risk-assessment experiments and her record must be carefully considered as well. NIH and the public must remain committed to continuous reevaluation of the NIH Guidelines as more and more is learned. I believe this action I am proposing is fully supported by the new information as well as the reassessment of prior information as described earlier in this decision.

Exempt All Experiments in E. coli K-12 From the Guidelines

Some called for the complete exemption from the NIH Guidelines of all recombinant DNA experiments using *E. coli* K-12 as the host.

The recommendation of the RAC was not, in fact, for complete exemption of such experiments. Three important safety features for these experiments that will not be exempt, but will according to the proposed decision form a special class under the Guidelines, are:

1. P1 Containment—Including the ban on mouth pipetting and the requirement that all biological wastes shall be decontaminated. Proper employment of P1 conditions eliminates the primary means of *E. coli* escape from the laboratory.

2. EK1—Allowing only *E. coli* K-12 strains and not allowing the use of conjugation proficient plasmids or generalized transducing phages. This greatly reduces the probability that any escaping *E. coli* K-12 would survive and transfer their recombinant DNA to other organisms.

3. IBC Oversight—Continuing local surveillance and registration of these experiments.

In addition, keeping these experiments under the Guidelines rather than exempting them means that any scale-up of the experiments beyond 10 liters will require prior NIH approval.

Treat Experiments Equally in which There Is or Is Not a Deliberate Attempt To Achieve Gene Expression

Some argued that recombinant DNA experiments should be treated no differently whether there is, or is not, a deliberate attempt to achieve gene expression.

In my Decision Document of July 1978, I wrote:

Although clearly the time has come to revise the original NIH Guidelines for Recombinant DNA Research, it is not the time to conclude that they are being altered in preparation for their early abandonment. Understanding of gene regulation and expression is increasing inexorably and at an awesome pace. We may predict that ways will be found to achieve and control the translation of foreign genes by a variety of hosts. As the barriers to translation are dropped, some of the larger promise of recombinant technology will be realized. In some proportion to the harvest of positive results, a capability must be maintained for observing any capacity of these experiments to yield harmful products, and for communicating this to all who have an interest in similar experiments.

It is now one year later, and more ways to assure gene expression are being found.

Some of the recent papers reporting on gene expression in *E. coli* of inserted recombinant DNA include:

L. Villa-Komaroff et al., A Bacterial Clone Synthesizing Proinsulin, *Proc. Natl. Acad. Sci. USA* 75, 3727, 1978.

T. H. Fraser and B. J. Bruce, Chicken Ovalbumin Is Synthesized and Excreted by *Escherichia coli*, *Proc. Natl. Acad. Sci. USA* 75, 5936, 1978.

D. V. Goeddel et al. Expression in *Escherichia coli* of Chemically Synthesized Genes for Human Insulin, *Proc. Natl. Acad. Sci. USA* 76, 106, 1979.

T. M. Roberts et al., A General Method for Maximizing the Expression of a Cloned Gene, *Proc. Natl. Acad. Sci. USA* 76, 760, 1979.

C. J. Burrell et al., Expression in *Escherichia coli* of Hepatitis B Virus DNA Sequences Cloned in Plasmid pBR322, *Nature* 279, 43, 1979.

D. V. Goeddel et al., Direct Expression in *Escherichia coli* of a DNA Sequence Coding for Human Growth Hormone, *Nature* 281, 544, 1979.

The RAC, at their September 6-7 meeting in discussing the "*E. coli* K-12/P1 Recommendation," grappled with the issue of "biologically active polypeptides" produced by *E. coli* K-12 carrying recombinant DNA. As discussed in Section III-B above, there is only a remote possibility that *E. coli* K-12 carrying recombinant DNA would escape, survive, compete, and implant in an environmental niche, etc. Were such an unlikely event to occur, however, an *E. coli* K-12 deliberately programmed to achieve eukaryotic gene expression could conceivably be a greater hazard than an *E. coli* K-12 not so endowed. Therefore, experiments in which there is a deliberate attempt to achieve gene expression continue to merit special attention. For these reasons, as discussed below in Section III-E, my proposed decision is to place a special requirement on any experiment in which there is a deliberate attempt to have the *E. coli* K-12 efficiently express a gene coding for a eukaryotic protein. For such an experiment, prior review and approval by the IBC would be required. This will allow the IBC to judge whether it wishes to require any added restrictions to be placed on the experiment, and to remain fully informed of its progress.

Include Ff Bacteriophages (Filamentous Single Strand Male Specific Bacteriophages Such As M13 and fd) With Lambda or Lambdoid Bacteriophages To Be Permissible Under the "E. coli K-12/P1 Recommendation"

The 1978 Guidelines define EK1 as follows: "The host is always *E. coli* K-12

or a derivative thereof, and the vectors include nonconjugative plasmids (e.g., pSC101, Co1E1, or derivatives thereof) and variants of bacteriophage, such as lambda. The *E. coli* K-12 hosts shall not contain conjugation-proficient plasmids, whether autonomous or integrated, or generalized transducing phages."

A memorandum of December 26, 1978, from the NIH Office of Recombinant DNA Activities to Institutional Biosafety Committees said, "The M13, fd, and other related single-strand bacteriophages . . . in conjunction with *E. coli* K-12 strains that do not contain conjugation-proficient plasmids (i.e., F-) are acceptable for experiments that require EK1 biological containment. Since the host strains are not the natural hosts, the means of infection would involve transfection."

At the RAC meeting of February 15-16, 1979, a motion passed by a vote of 20 to 1, with 1 abstention, that "Conjugation-deficient mutants, such as the *traD* and *trai* mutants of the F factor may be used with the Ff bacteriophages if they have been shown to exhibit low levels of transfer (of the order of 10^{-5} or less) and also have low reversion rates (such as found for deletion or double-mutants)." This recommendation was accepted by NIH and transmitted by ORDA to IBCs on April 23.

(At the RAC meeting of May 21-23, 1979, a proposal to allow the use of bacteriophage vectors in *E. coli* K-12 hosts containing conjugation-proficient plasmids was rejected by a vote of 10 to 4, with 5 abstentions.)

Thus today EK1 experiments are being conducted under the NIH Guidelines using Ff bacteriophages.

The "*E. coli* K-12/P1 Recommendation" as passed by the RAC on September 6 includes the words "lambda or lambdoid bacteriophages," without mention of Ff bacteriophages. One alternative which I considered was to add the words "or Ff" before "bacteriophages." However, in the absence of a specific recommendation from the RAC on this point, and because Ff bacteriophages have a broader host range than lambda or lambdoid bacteriophages, I am not adopting this alternative.

What shall be the status then of ongoing EK1 experiments involving Ff bacteriophages when the new Guidelines are promulgated? At the time of impending transition from the 1976 to the 1978 Guidelines, a memorandum was sent from ORDA to IBCs and Principal Investigators ("Transition to Revised Guidelines for Recombinant DNA Research") which allowed certain on-going experiments to continue at the

containment levels of the 1976 Guidelines.

In accordance with this precedent, I propose a similar policy be followed in the transition from the 1978 to the new Guidelines. Thus an investigator using an Ff bacteriophage could continue at the stipulated containment level of the 1978 Guidelines. For example, for the cloning of primate DNA in *E. coli* K-12, currently proceeding at the P3 + EK1 containment level, the experiment may continue using Ff bacteriophage at EK1 but must also remain at the P3 containment level.

I will ask the RAC to consider the use of Ff bacteriophages again at their next meeting.

Keep National Registration and Oversight of These Experiments

Some argued that Memoranda of Understanding and Agreement (MUA) covering the experiments falling under the "*E. coli* K-12/P1 Recommendation" should continue to be sent to NIH for national registration and oversight of these experiments.

In my decision document of July 1978, I wrote:

In view of the impossibility of Federal surveillance to enforce these standards externally, I feel it is essential to increase the authority and responsibility of the local institution . . . Primary responsibility for compliance with the rules must be located where the work is done. There it must be shared fully by principal investigators, those who work in their laboratories, institutional biosafety committees, and the institutional leaders. The NIH Office of Recombinant DNA Activities (ORDA) should be relieved of its burden of obligatory prior approval of certain experiments, so that it can better carry out, along with the RAC, two central functions. These are the continuing synthesis and interpretation of the Guidelines, and the maintenance of full communication among all who must use them.

I remain committed to shifting responsibility to local institutions for adherence to uniform, sensible guidelines. We are dealing in this decision with a class of experiments judged to be of minimal risk. There is the possibility that some aspect of some future experiment in this class may yield information relevant to safety that should be transmitted to all laboratories where similar experiments are being conducted. The Guidelines (Sections IV-D-1; IV-D-3-e and IV-D-5-a-(2)) still require that "any significant problems with . . . the Guidelines and significant research-related accidents and illnesses" are to be reported to ORDA. ORDA can then quickly notify all IBCs; and IBCs, having a registry of such experiments, can take appropriate actions without delay. The transmission

to ORDA of registration of experiments in this class does not enhance safety or otherwise serve the public interest. The relief from central data-handling for these experiments will leave ORDA free to perform other functions that are more likely to assure that use of recombinant DNA techniques is safe.

III-E. Proposed Decision of the Director, NIH On The "E. coli K-12/P1 Recommendation"

The "*E. coli* K-12/P1 Recommendation," as passed by the RAC on September 6, recommends that the experiments described in the proposal be "exempted from the Guidelines." Yet it also specifies that "P1 containment shall be used." In addition, it requires that these experiments be registered with the IBC but "with no requirement for review by the IBC prior to initiation of experiments."

Currently, exempt experiments (described in Section I-E of the Guidelines) do not have any containment level specified and are not required to be registered with the IBC.

Currently, experiments described in Part III of the Guidelines have containment levels specified and are required not only to be registered with the IBC but also to be approved by the IBC prior to initiation of the experiment. (In addition, an MUA must be submitted to NIH for approval, although for most experiments the project can proceed upon IBC approval, without prior approval by NIH.)

I believe the term "exempt experiment" as currently used in Section I-E of the Guidelines should be used only for experiments for which no containment level is specified and for which no registration with the IBC is required. Therefore, I propose not to accept the part of the "*E. coli* K-12/P1 Recommendation" which refers to the described experiments as exempt. Instead, my proposed decision is to describe the experiments covered in the "*E. coli* K-12/P1 Recommendation" in a new Section which to be added to the Guidelines, called Section III-0, as follows:

III-0. Classification of Experiments Using the *E. coli* K-12 Host-Vector Systems. Most recombinant DNA experiments currently being done employ *E. coli* K-12 host-vector systems. These are the systems for which we have the most experience and knowledge.

Some experiments using *E. coli* K-12 host-vector systems are prohibited (see Section I-D).

Some experiments using *E. coli* K-12 host-vector systems are exempt from the Guidelines (see Sections I-E).

Other experiments using *E. coli* K-12 shall use P1 physical containment and, except as

specified in the last paragraph of this section, an EK1 host-vector system (i.e., (a) the host shall not contain conjugation-proficient plasmids or generalized transducing phages, and (b) lambda or lambdoid bacteriophages or non-conjugative plasmids shall be used as vectors). For these experiments no Memorandum of Understanding and Agreement (MUA) as described in Section IV-D-1-c need be submitted, nor is any registration with NIH necessary. However, for these experiments, prior to their initiation, investigators must submit to their Institutional Biosafety Committee (IBC) a registration document that contains a description of (a) the source(s) of DNA, (b) the nature of the inserted DNA sequences, and (c) the hosts and vectors to be used. This registration document must be dated and signed by the investigator and filed only with the local IBC. The IBC shall review all such proposals but such review is not required prior to initiation of experiments. An exception, however, which does require prior review and approval by the IBC is any experiment in which there is a deliberate attempt to have the *E. coli* K-12 efficiently express any gene coding for a eukaryotic protein.

Experiments involving the insertion into *E. coli* K-12 of DNA from prokaryotes that exchange genetic information with *E. coli* by known physiological processes will be exempted from these Guidelines if they appear on the "list of exchangers" set forth in Appendix A (see Section I-E-4).

For those not on the Appendix A list but which exchange genetic information [35] with *E. coli*, experiments may be performed with any *E. coli* K-12 vector (e.g. conjugative plasmids). When a non-conjugative vector is used, the *E. coli* K-12 host may contain conjugation-proficient plasmids, either autonomous or integrated, or generalized transducing phages.

The first two sentences of Section III-0 are moved from where they appear as the first two sentences of Section III-A in the 1978 Guidelines.

The next two sentences refer to the fact that some experiments using *E. coli* K-12 are prohibited (Section I-D) and that some are truly exempt from the Guidelines (Section I-E). The prohibitions override Section III-0; the six prohibitions are I-D-1 ("pathogenic organisms"), I-D-2 ("potent toxins"), I-D-3 ("plant pathogens"), I-D-4 ("deliberate release"), I-D-5 ("drug resistance trait"), and I-D-6 ("large scale").

Next in Section III-0 comes a rephrasing of the "*E. coli* K-12/P1 Recommendation," setting the containment level as P1 + EK1 for these experiments. Also included for these experiments is the requirement for registration with, but not prior approval by, the IBC, for most experiments and the statement that no MUA or other form of registration need be submitted to NIH. The requirement for IBC prior approval has been added for

experiments in which there is a deliberate attempt to have the *E. coli* K-12 efficiently express any gene coding for a eukaryotic protein.

The last two paragraphs of Section III-0 are a rephrasing of what appears as part of Section III-A-1-b-(1) of the 1978 Guidelines, including incorporation of rewording, as discussed below, in the first item in Part IV of this announcement.

Within Section IV of the Guidelines, a note has been inserted in Section IV-D-1-c reminding the reader that "no MUA is required for experiments described in Section III-0," and a note has been inserted in Section IV-D-5-a-(1) reminding the reader that "no prior approval by the IBC is required for most experiments described in Section III-0."

At places in the Guidelines describing "return to host of origin" type experiments (i.e., Sections III-B-2, III-C-5, III-C-6, III-C-7-a, and III-C-7-b), the phrase "appropriate containment" has been replaced by "P1."

Section III-A of the Guidelines, and its subsections, previously referring to experiments using *E. coli* K-12 as the host have been rewritten to refer to certain other certified HV1 and HV2 systems, as listed in Appendix D of the November 1979 Guidelines.

It was the intent of the RAC that "the principle of equivalency of HV systems with EK systems applies at the present time only to the setting of containment levels for shotgun experiments. It does not apply at the present time to lowering of containment levels for characterized or purified DNA preparations and clones, to returning DNA segments to non-HV1 host of origin, etc." (Federal Register, July 20, 1979). Therefore, changes have been made in Section III-A-1-a-(1), III-A-3-a, III-A-3-b, IV-D-1-c-(3), IV-D-1-e, and IV-E-1-b-(3)-(e), indicating that lowering of containment levels for characterized or purified DNA preparations or clones requires prior approval by the NIH and that IBC approval alone is no longer sufficient. In accordance with Section IV-E-1-b of the NIH Guidelines and based on the extensive analysis given above, I find that these proposed actions on the "*E. coli* K-12/P1 Recommendation" comply with the Guidelines and present no significant risk to health or the environment.

Appendix A gives the membership at the Recombinant DNA Advisory Committee at the May 1979 meeting; Appendix B gives the membership at the September 1979 meeting.

IV. Other Recommendations on "Major Actions" Made at the September 6-7, 1979, RAC Meeting

In addition to the "*E. coli* K-12/P1 Recommendation" discussed above, five other recommendations on "major actions" were made at the September 6-7 RAC meeting. These are discussed below, and my proposed action on them is given. In accordance with Section IV-E-1-b of the NIH Guidelines, I find that these proposed actions comply with the Guidelines and present no significant risk to health or the environment.

Proposed Amendment of Sections II-D-1-a-(1) and III-A-1-b-(1) of the 1978 Guidelines

In response to a suggestion made in a letter of May 16, 1979, from Dr. Nickolas J. Panopoulos, of the University of California at Berkeley, proposed changes in the Guidelines were published for comment in the Federal Register on July 31, 1979, as follows:

1. Proposed to be inserted at the end of Section II-D-1-a-(1) of the Guidelines were the words "except as specified under Section III-A-1-b-(1)."

2. Proposed to be inserted at the end of section III-A-1-b-(1) of the Guidelines were the words "When a non-conjugative vector is used, the *E. coli* K-12 host may contain conjugative proficient plasmids, either autonomous or integrated, or generalized transducing phages. In general, for experiments in this category, the *E. coli* K-12 host may contain such plasmids or phages provided that the physical containment level is raised one step."

During the 30-day comment period, no comments were received.

At the RAC meeting on September 6-7, 1979, this item was discussed. A motion was passed by the RAC by a vote of 12 to 0 to:

1. Insert at the end of Section II-D-1-a-(1) of the 1978 Guidelines the words "except as specified under Section III-A-1-b-(1)"; and

2. Insert prior to the last sentence of Section II-A-1-b-(1) of the 1978 Guidelines, the words "When a non-conjugative vector is used, the *E. coli* K-12 host may contain conjugation proficient plasmids, either autonomous or integrated, or generalized transducing phages."

I propose to accept these recommendations. However, due to my proposed action on the "*E. coli* K-12/P1 Recommendation" (as described above in Part III-E of this announcement), further changes are necessary in incorporating these recommendations into the proposed revised NIH Guidelines. Thus the insert at the end of

Section II-D-1-a-(1) reads, "except as specified in Section III-0," and the added words "When a nonconjugative vector is used, the *E. coli* K-12 host may contain conjugation-proficient plasmids, either autonomous or integrated, or generalized transducing phages" appear in Section III-0.

Proposed Exemption for *Pseudomonas putida* and *Pseudomonas fluorescens*

At its May 21-23, 1979, meeting, the RAC considered a request by Dr. N. Ornston of Yale University to add *Pseudomonas putida* and *Pseudomonas fluorescens* to the exempt list in Appendix A of gram-negative organisms that exchange DNA by known physiological processes. The RAC, at that time, voted 17 to 1, with 1 abstention, to defer action on the proposal, since several members felt that the transduction data were incomplete, and an error was made in the Federal Register notice. A request for additional data on the reversion frequencies for the transduced markers was made on recommending deferment.

After receipt of additional documentation on the chromosomal genetics of *Pseudomonas*, the following notice was placed in the Federal Register on July 31, 1979, for comment:

Dr. N. Ornston of Yale University has proposed, in accord with Section I-E-4 of the Guidelines, that *Pseudomonas putida* and *Pseudomonas fluorescens* be added to the exempt list in Appendix A of gram-negative organisms that exchange DNA by known physiological processes. Further information documenting the exchange of genetic information between these two species and those in Appendix A is available from the Office of Recombinant DNA Activities.

No comments were received during the 30-day comment period.

At the September 6-7 RAC meeting the data on exchange and homology were discussed and a motion to add *Pseudomonas putida* and *Pseudomonas fluorescens* to the Appendix A list passed by a vote of 11 to 0, with 3 abstentions.

I propose to accept this recommendation and have added *Pseudomonas putida* and *Pseudomonas fluorescens* to Sublist A in Appendix A, of the proposed revised Guidelines.

Cloning in *Bacillus Subtilis* and *Streptomyces Coelicolor*

In response to a request from Dr. Stanley Cohen of Stanford University, the following proposal was published for comment in the Federal Register on July 31, 1979:

(a) *Bacillus subtilis* strains that do not carry an asporogenic mutation can be used as hosts specifically for the cloning of DNA

derived from *E. coli* K-12 and *Streptomyces coelicolor* using NIH-approved *Staphylococcus aureus* plasmids as vectors under P2 conditions.

(b) *Streptomyces coelicolor* can be used as a host for the cloning of DNA derived from *B. subtilis*, *E. coli* K-12, or from *S. aureus* vectors that have been approved for use in *B. subtilis* under P2 conditions.

During the 30-day comment period, no comments were received.

This proposal had been discussed at the February and May 1979 RAC meetings. At the September RAC meeting, after discussion of the safety of these systems including the issue of spore formation, the final votes on these proposals were 9 in favor, none opposed, with 8 abstentions, to approve part (b) dealing with cloning in *Streptomyces coelicolor*, and 8 in favor, 5 opposed, with 5 abstentions, to approve part (a) dealing with cloning in *Bacillus subtilis*.

I propose to accept these recommendations, and they have been inserted into Appendix E of the proposed revised Guidelines.

Use of Agrobacterium Tumefaciens as a Host-Vector System

The following notice appeared for comment in the *Federal Register* on July 31, 1979:

At its May 21-23, 1979, meeting, the RAC recommended approval, at the P3 level of physical containment, of specific experiments involving introduction of well-characterized fragments of eukaryotic DNA into *Agrobacterium tumefaciens* carrying a Ti plasmid, using an EK2 plasmid vector coupled to a fragment of the Ti plasmid and/or the origin of replication of a cryptic *A. tumefaciens* plasmid, and introduction of these bacteria into plant parts or cells in culture under P3 conditions. Approval is now requested by Dr. M. D. Chilton for modification of the experimental procedure as follows:

Cloned desired fragments from any non-prohibited source may be transferred into *Agrobacterium tumefaciens* containing a Ti plasmid (or derivatives thereof), using a non-conjugative *E. coli* plasmid vector coupled to a fragment of the Ti plasmid and/or the origin of replication of an *Agrobacterium* plasmid, under containment conditions one step higher than would be required for the desired DNA in EK1 or HV1 systems. Transfer into plant parts or cells in culture would be permitted at the same containment level (one step higher).

During the 30-day comment period, no comments were received.

At the September RAC meeting, after discussion of the safety of this system, a motion to approve this proposal passed by a vote of 9 in favor, 8 opposed, with 2 abstentions.

I propose to accept this recommendation and have inserted into Appendix E of the proposed revised

Guidelines the text as it appeared in the July 31 *Federal Register*—i.e., "Cloned desired fragments. . . (one step higher)"—with one change in wording. This change necessitated by my proposed action on the "*E. coli* K-12/P1 Recommendation" (see Part III of this announcement above), is to substitute for the words ". . . in EK1 or HV1 systems . . ." the words ". . . in HV1 systems (i.e., one step higher physical containment than that specified in the subsections of Section III-A) . . ."

Proposed Supplement to the NIH Guidelines

The 1978 Guidelines say in Section IV-F-4, "[Provisions for protection of proprietary information as permitted under current DHEW authorities will be proposed as a future supplement to these Guidelines.]"

On August 3, 1979, there was published in the *Federal Register*, for public comment, a proposed supplement to the NIH Guidelines.

The August 3 *Federal Register* notice first contained background information as follows:

On December 22, 1978, the Director, National Institutes of Health, with the approval of the Assistant Secretary for Health and the Secretary of Health, Education, and Welfare, issued revised Guidelines for Research Involving Recombinant DNA Molecules [43 FR 80108]. These Guidelines were accompanied in the *Federal Register* by a Notice of Intent to Propose Regulations issued by the Food and Drug Administration. In addition, the Secretary sent letters to Administrator Douglas Costle, Environmental Protection Agency, and to Secretary of Agriculture Bob Bergland, requesting comparable actions to ensure a commonality of standards throughout the private sector. In July the Secretary sent a similar request to Secretary of Labor Ray Marshall.

Several responses to the FDA notice questioned that agency's legal authority to regulate private research in this field. In view of these comments, NIH Director Donald S. Fredrickson and the Commissioner of Food and Drugs, Donald Kennedy, developed a draft supplement to the NIH Guidelines that would extend them on a voluntary basis to industry. This draft was reviewed by Peter Libassi, then General Counsel for the Department, who also consulted with representatives from the pharmaceutical industry and from public interest and environmental organizations. The representatives from the pharmaceutical industry considered the supplement to provide a feasible basis for voluntary compliance; the representatives from the other groups considered a voluntary system insufficient and urged that mandatory compliance be achieved through legislation or regulation.

In light of those discussions it was agreed that the draft supplement prepared by NIH

and FDA should also be reviewed by the Federal Interagency Advisory Committee on Recombinant DNA Research which includes all relevant Federal research and regulatory agencies. This Committee, created in October 1976 to consider extension of the Guidelines nationally, had recommended in March 1977 that legislation be developed. On July 16, 1979, the Committee met to consider the draft supplement and alternative approaches to extent the revised NIH Guidelines to the private sector. It was the Committee's unanimous opinion that NIH should proceed to publish for public comment the draft supplement to the NIH Guidelines. The conclusion was not unanimous that the voluntary approach would achieve complete compliance within the private sector.

On the basis of the recommendations by the Interagency Committee, the Director, NIH, invites public comment on the proposed supplement to the NIH Guidelines, which is set forth below * * *

The August 3 *Federal Register* notice then gave the text of proposed sections to be added to the Guidelines. The full text is not repeated in this announcement. The headings of the proposed sections are:

IV-G-5. Voluntary Compliance.; VI. Voluntary Compliance.; VI-A. Basic Policy.; VI-B. IBC Approval; VI-C. Registration.; VI-D. Certification of Host-Vector Systems.; VI-E. Request for Exceptions.; and VI-F. Protection of Proprietary Data.

During the 30-day comment period, five letters were received.

A representative of the AFL-CIO wrote:

We firmly believe that regulatory authority over health and safety of workers must be the responsibility of the Occupational Safety and Health Administration. Promulgation of your inadequate and impotent Guideline additions can only hamper efforts to provide proper oversight by OSHA. Therefore, these Guideline sections should not be adopted. NIH has no business intruding upon the affairs of non-grantees or other government agencies.

A representative of the Environmental Defense Fund wrote:

In the absence of statutory authority enabling NIH inspection and enforcement of industrial experiments and providing for stiff penalties for violations, approval is a meaningless exercise. Indeed, its only benefit is to the industrial sponsor, who is then free to proclaim that its experiments are safe and above public concern. From a political standpoint, we fear that a voluntary program, no matter how insufficient, will provide a public relations weapon to industry and an argument against mandatory control * * * voluntary compliance programs have never worked and never will.

Dr. Susan Wright wrote that the "proposal is ill-advise * * * 'voluntary compliance' means that the private sector will obey the guidelines when it is

in its interests to do so and not otherwise."

A representative of Genex Corporation wrote concerning the requirement for membership on Institutional Biosafety Committees. He submitted proposed wording to be inserted in Section VI-B.

The New York State Commissioner of Health wrote, "It seems clear that Federal legislation offers the best prospect of establishing a uniform, enforceable set of minimum standards. The individual states could retain the option of setting more stringent requirements."

At the September RAC meeting, there was considerable discussion of the proposed supplement. John Adams of the Pharmaceutical Manufacturers Association indicated that the PMA member firms engaged in recombinant DNA research fully endorse the supplement and will fully comply with the Guidelines. In reply to a question from the RAC, Dr. Irving Johnson of Eli Lilly and Company indicated that Lilly's IBC had three members not affiliated with the company among its nine IBC members. Representatives of Genentech, Eli Lilly and Company, and Genex said their companies would comply with the Guidelines.

One RAC member said he favored mandatory compliance as the long term solution but thought it was fine to begin with a voluntary system. Others spoke strongly in favor of the supplement, to initiate a test period to see if industry does indeed comply. Representatives of the National Science Foundation and the National Institute for Occupational Safety and Health reviewed the unanimous recommendation of the Interagency Committee on Recombinant DNA Research to proceed with the voluntary supplement. A representative of the Office of Science and Technology Policy endorsed the proposal.

A motion to accept Section IV-G-5 and Part VI as they appeared in the Federal Register on August 3 passed with a vote of 11 in favor, none opposed, with 4 abstentions.

I propose to accept these recommendations and have added these sections to the proposed revised Guidelines.

Appendix C gives the membership of the Interagency Committee on Recombinant DNA Research.

Appendix A—Membership of the Recombinant DNA Advisory Committee at the May 1979 Meeting

Recombinant DNA Advisory Committee

SETLOW, Jane K., Ph.D., (Chairman),
Biologist, Brookhaven National Laboratory,

Upton, Long Island, New York 11973, 516-345-3420.

AHMED, Abdul Karim, Ph.D., Senior Staff Scientist, Natural Resources Defense Council, Inc., 122 East 42nd Street, New York, New York 10017, 212-949-0049.

BALTIMORE, David, Ph.D., Professor of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, 617-253-6410.

BROADBENT, Francis E., Ph.D., Professor of Soil Microbiology, Department of Land, Air and Water Resources, University of California, Davis, California 95616, 916-752-0198.

CAMPBELL, Allan M., Ph.D., Professor, Department of Biology, Stanford University, Stanford, California 94305, 415-497-1170.

CASON, Zelma, Supervisor of Cytopathology Laboratory, University of Mississippi Medical Center, Jackson, Mississippi 39216, 601-968-5547.

DAY, Peter R., Ph.D., Chief, Division of Genetics, Connecticut Agricultural Experiment Station, New Haven, Connecticut 06504, 203-789-7258.

GOLDSTEIN, Richard, Ph.D., Assistant Professor of Microbiology and Molecular Genetics, Harvard Medical School, Boston, Massachusetts 02115, 617-732-1911.

GOTTESMAN, Susan K., Ph.D., Senior Investigator, Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014, 301-498-3524.

HORNICK, Richard B., M.D., Chairman, Department of Medicine, University of Rochester School of Medicine, Rochester, New York 14642, 716-275-2871.

KING, Patricia A., J.D., Professor of Law, Georgetown University Law Center, Washington, D.C. 20001, 202-624-8295.

KRIMSKY, Sheldon, Ph.D., Acting Director, Program in Urban Social and Environmental Policy, Tufts University, Medford, Massachusetts 02155, 617-628-5000 x8159.

KUTTER, Elizabeth M., Ph.D., c/o Department of Nutrition, University of California, Davis, California 75616, 916-752-3389.

NOVICK, Richard P., M.D., Chairman of Plasmid Biology, Public Health Research Institute, New York, New York 10016, 212-481-0740.

PARKINSON, David K., B.M., B.Ch., Associate Professor of Occupational Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, 412-624-3041.

PINON, Ramon, Ph.D., Assistant Professor of Biology, B-022 Bonner Hall, University of California, San Diego, California 92093, 714-452-2452.

PROCTOR, Samuel D., Ph.D., Professor of Education, Rutgers University, New Brunswick, New Jersey 08903, 201-932-7389.

REDFORD, Emmette S., Ph.D., LL.D. (79), Ashbel Smith Professor of Government and Public Affairs, Lyndon B. Johnson School of Public Affairs, University of Texas at Austin, Austin, Texas 78712, 512-471-4962 x234.

ROWE, Wallace P., M.D., Chief, Laboratory of Viral Diseases, National Institute of

Allergy & Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20014, 301-498-2813.

SPIZIZEN, John, Ph.D., Member and Chairman, Department of Microbiology, Scripps Clinic & Research Foundation, La Jolla, California 92037, 714-454-3881 x387

THORNTON, Ray H., J.D., Executive Director, Joint Educational Consortium, Henderson State University, Cuachita Baptist University, P.O. Box 499, Arkadelphia, Arkansas 71923, 501-246-9283

WALTERS, LeRoy, Ph.D., Director, Center for Bioethics, Kennedy Institute, Georgetown University, Washington, D.C. 20057, 202-625-2371.

WILLIAMS, Luther S., Ph.D., Associate Professor of Biology and Assistant Provost, Department of Biological Sciences, Purdue University, West Lafayette, Indiana 47907, 317-493-0211.

YOUNG, Frank E., M.D., Ph.D., Dean, School of Medicine & Dentistry, University of Rochester, Rochester, New York 14642, 716-275-3407.

ZAITLIN, Milton, Ph.D., Professor, Department of Plant Pathology, Cornell University, Ithaca, New York 14853, 607-256-3105.

GARTLAND, William J., Jr., Ph.D., (Executive Secretary), Director, Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, Maryland 20014, 301-496-6051.

Recombinant DNA Advisory Committee Non-Voting Representatives

Center for Disease Control

LaMotte, Louis C., Ph.D., Director, Licensure in Proficiency Testing Division, Bureau of Laboratories, Center for Disease Control, Atlanta, Georgia 30333, 404-329-3824.

Department of Agriculture

TOLIN, Sue A., Ph.D., Science and Education Administration, Cooperative Research, U.S. Department of Agriculture, Washington, D.C. 20250, 202-447-5741.

FULKERSON, John F., Ph.D. (ALT), Science and Education Administration, Cooperative Research, U.S. Department of Agriculture, Washington, D.C. 20250, 202-447-5741.

Department of Commerce

GALLER, Sidney R., Ph.D., Room 3425, U.S. Department of Commerce, Washington, D.C. 20230, 202-377-4335.

GORDON, George S., Ph.D., (ALT), Room 3424, U.S. Department of Commerce, Washington, D.C. 20230, 202-377-2565.

Department of Energy

DUDA, George Ph.D., Division of Biomedical and Environmental Research, U.S. Department of Energy, Washington, D.C. 20545, 202-353-3651.

EDINGTON, Charles W., Ph.D. (ALT), Deputy Director, Office of Health and Environmental Research, U.S. Department of Energy, Washington, D.C. 20250, 202-353-3251.

Department of the Interior

PIMENTEL, Mariano B., Ph.D., Room 7045, U.S. Department of the Interior, Washington, D.C. 20240, 202-343-2081.

Department of State

WALSH, William J., III, Biomedical Research Liaison and Health Affairs Officer, Oceans and International Environmental and Scientific Affairs, U.S. Department of State, Washington, D.C. 20520, 202-632-4824.

Department of Transportation

CUSHMAC, George E., Ph.D., Chemist, Research and Special Programs Administration, U.S. Department of Transportation, Washington, D.C. 20590, 202-755-4908.

Food and Drug Administration

GRYDER, Rosa, Ph.D., Staff Science Advisor, HFY-311, Food and Drug Administration 56, Rockville, Maryland 20857, 301-433-4491.

National Aeronautics and Space Administration

YOUNG, Richard S., Ph.D., Director of Planetary Biology, National Aeronautics and Space Administration, Washington, D.C. 20546, 202-755-3732.

National Science Foundation

LEWIS, Herman W., Ph.D., Senior Scientist for Recombinant DNA, Division of Physiology, Cellular and Molecular Biology, National Science Foundation, Washington, D.C. 20550, 202-632-4200.

HARRIMAN, Philip Ph.D. (ALT), Program Director for Genetic Biology, Room 326, National Science Foundation, Washington, D.C. 20550, 202-632-5985.

Veterans Administration

SCHULTZ, Jane S., Ph.D., Chief, Program Development and Review Division, U.S. Veterans Administration, 810 Vermont Avenue, N.W., Washington, D.C. 20420, 202-389-5065.

BERMAN, Howard M., Ph.D. (ALT), Health Scientist, Program Development and Review Division, 810 Vermont Avenue, N.W., Washington, D.C. 20420, 202-389-5065.

Department of Labor

PICCIANO, Dante, Ph.D., Office of Carcinogen Identification and Classification, Occupational Safety and Health Administration, U.S. Department of Labor, Washington, D.C. 20210, 202-523-7177.

Recombinant DNA Advisory Committee**Liaison Representatives**

HEDRICH, Richard, Ph.D., Coordination Program of Science Technology & Human Value, National Endowment for the Humanities, Washington, D.C. 20506, 202-382-5998.

WEISS, Daniel L., M.D., Assembly of Life Sciences, National Academy of Sciences, Washington, D.C. 20418, 202-389-6315.

Appendix B—Membership of the Recombinant DNA Advisory Committee at the September 1979 Meeting**Recombinant DNA Advisory Committee****Chairman**

SETLOW, Jane K., Ph.D., Biologist, Brookhaven National Laboratory, Upton,

Long Island, New York 11973, 516-345-3420.

AHMED, Abdul Karim, Ph.D., Senior staff Scientist, Natural Resources Defense Council, Inc., 122 East 42nd Street, New York, New York 10017, 212-949-0049.

BALTIMORE, David, Ph.D., Professor of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, 617-253-6410.

BRILLE, Winston, Jr., Ph.D., Professor of Bacteriology, Department of Bacteriology, University of Wisconsin, Madison, Wisconsin 53706, 608-282-3567.

BROADBENT, Francis E., Ph.D., Professor of Soil Microbiology, Department of Land, Air and Water Resources, University of California, Davis, California 95616, 916-752-0198.

CAMPBELL, Allan M., Ph.D., Professor, Department of Biology, Stanford University, Stanford, California 94305, 415-497-1170.

CASON, Zelma, Supervisor of Cytopathology Laboratory, University of Mississippi Medical Center, Jackson, Mississippi 39216, 601-968-5547.

GOLDSTEIN, Richard, Ph.D., Assistant Professor of Microbiology and Molecular Genetics, Harvard Medical School, Boston, Massachusetts 02115, 617-732-1911.

GOTTESMAN, Susan K., Ph.D., Senior Investigator, Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, 301-496-3524.

HARRIS, Jean L., M.D., Secretary of Human Resources, Commonwealth of Virginia, Office of Governor, Post Office Box 1475, Richmond, Virginia 23212, 804-358-1170.

KING, Patricia A., J.D., Professor of Law, Georgetown University Law Center, Washington, D.C. 20001, 202-624-8295.

KRIMSKY, Sheldon, Ph.D., Acting Director, Program in Urban Social and Environmental Policy, Tufts University, Medford, Massachusetts 02155, 617-828-5000, x8159.

MAAS, Werner K., Ph.D., Professor of Microbiology, Department of Microbiology, New York University School of Medicine, New York, New York 10016, 212-679-3200, x2319.

MASON, James O., M.D., Dr. P.H., Executive Director, Utah State Department of Health, Post Office Box 2500, Salt Lake City, Utah 84110, 801-533-8111.

NIGHTINGALE, Elena O., M.D., Ph.D., Director, Division of Health Promotion and Disease and Senior Professional Associate, Institute of Medicine, National Academy of Sciences, Washington, D.C. 20418, 202-389-8721.

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PROCTOR, Samuel D., Ph.D., Professor of Education, Rutgers University, New

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THORNTON, Ray H., J.D., Executive Director, Joint Educational Consortium, Henderson State University, Ouachita Baptist University, P.O. Box 499, Arkadelphia, Arkansas 71923, 501-246-9283.

WALTERS, LeRoy, Ph.D., Director, Center for Bioethics, Kennedy Institute, Georgetown University, Washington, D.C. 20057, 202-625-2371.

WILLIAMS, Luthur S., Ph.D., Professor of Biology and Assistant Provost, Department of Biological Sciences, Purdue University, West Lafayette, Indiana 47907, 317-493-0211.

YOUNG, Frank E., M.D., Ph.D., Dean, School of Medicine & Dentistry, University of Rochester, Rochester, New York 14642, 716-275-3407.

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Executive Secretary

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Additional Announcement of the Director, NIH

Section IV-E-1-b-(3)-(d) of the Guidelines gives responsibility to the Director, NIH, for "authorizing, under procedures specified by the RAC, large-scale experiments (i.e., involving more than 10 liters of culture) for recombinant DNAs that are rigorously characterized and free of harmful sequences."

On October 5, 1979, the Director, NIH, on the recommendation of the Recombinant DNA Advisory Committee, approved a request from Lilly Research Laboratories for the lowering of containment and large-scale culture of EK1 host-vector systems carrying the chemically synthesized insulin A chain and B chain separately. The request was approved with the understanding that Lilly Research Laboratories have agreed to permit an observer, designated by NIH, to visit the facilities if NIH should choose to inspect the site.

The principal investigator is Dr. Lawrence E. Day. The work is to be done, as stipulated in the submission by Lilly Research Laboratories, in a "P2 laboratory containing fermenters designed and pretested to totally contain the organisms until they are chemically or physically killed at the end of each fermentation . . . at the plant facilities at 1200 South Kentucky Avenue, Indianapolis, Indiana, 46206."

Dated: November 26, 1979.

Donald S. Fredrickson,
Director National Institutes of Health.

[FR Doc. 79-38842 Filed 11-29-79; 8:45 am]

BILLING CODE 4110-08-M

RECOMBINANT ODYSSEY III

December 1979

As part of a visit to the Committee on Medical Research (CRM) of the Commission of the European Communities (COEC), arising from an invitation from CRM earlier in the year, I left Washington the evening of December 5, accompanied by Dr. Joseph Quinn, Deputy Director of FIC. We arrived in London on December 6, emplaned for Brussels, arriving there at noon. We were met by a car from the Embassy motor pool and taken briefly to the Hyatt Regency Hotel, where we changed clothes and left immediately for the Argenteuil residence of Princess Lilian of Belgium and her husband, King Leopold. Arriving a bare ten minutes late, we entered the library at the north end of the chateau, where, warmed by a fireplace and the floor-to-ceiling Moroccan bindings of the Graaf de Flamande (Leopold's grandfather), were gathered the Princess; her daughter, Daphne (about 30); Professor Luigi Donato, President of CRM; and Professor C. Van Apersele, a renal physiologist at the University. I reminded the Princess that we had last met in 1962, when she and the King, in the company of Eunice Shriver, had visited NIH, lunched with Jim Shannon (per Eunice), and attended rounds. I was the Clinical Director of NHI then, and Lilian commanded the afternoon with her knowledge of heart surgery and surgeons--her son had been one of Robert Gross' successes--a coarctation, I believe. It was at Mike DeBakey's request that I lunched with the Princess on the occasion, particularly to discuss her Foundation. We never got to this subject, however, as we ranged widely over gossip about surgeons, questions and lofty schemes for attracting multinational patronage for research in the life sciences. From Argenteuil we went to the office of the new U.S. Ambassador Enders at USEC (America's new ambassador to the European Community). Enders is a tall, bright, effective man who listened to our appraisal of medical research in the U.S. and Europe, and the nuances of scientific diplomacy. We urged upon him a maximum of informality and a minimum of arrangements, leaving the scientists to enjoy their subjects more and agendas less. He seemed amenable, doubtless to some concern of his staff--his predecessor had been a "bear" for more formal agreements, reports, and steering groups. Ramsey, the scientific staff man, somewhat gleefully described the general strike expected to paralyze Brussels next day. (We ordered a car from Hertz to drive to Paris.) The next morning, we found the streetcars no longer running, a few buses on the routes, taxis available, and the usual confusion as to how much of a strike was in effect, abounded. Could one even get a car? The airports were reported to be open, so we delayed the car order and, in fact, canceled it later in the morning as the airport continued operating.

The CRM meeting was preceded by a briefing from Luigi Donato (a respiratory physiologist from Pisa) who had just been elected to serve one further year as President of CRM, a special extension of the prescribed term. He was accompanied by Mr. Van Hoeck, the quintessential Eurocrat, who is staff of Dr. Gunter Schuster, Director General for Research Science and Education. (We would meet Schuster later that day.) The CRM should not be confused with the EMRC (the European Medical Research Councils group), which is headed by Dr. Henry Danielsson and met in Bethesda in April of this year with NIH as host. The EMRC group includes 16 countries, more than the 9 in EEC, even though some individuals serve on both bodies, viz., Halter from Belgium. The CRM is not having an easy time of creating an ecumenical research movement in Europe. The founding treaty is heavy on "economic" unity, says nothing about biomedical research, or even health, except that implicit in the common effort for "general good" of the people. All joint decisions of CRM have to be unanimous; and currently Denmark (the catalyst for unity in EMRC) is refusing to study suicide as one of the generally agreed topics of all-European Community research. There is no budget for research to speak of. The CRM meeting was full of courtesies and amenities, but not long on research ideation. Another proposed general problem is Stress and Adaptation. The U.S. has joined the CRM, at the latter's invitation in three very specific subjects: extra-corporeal oxygenation, cellular aging, and congenital anomalies. They have asked us to name someone to help them in design of the Stress program. I was asked, and gave some lengthy opinions on their program, on health services research, and many other topics. I discussed NIH "search for consensus" activities and suggested we have a joint exercise next year. They were interested in this and we discussed, at length, possible topics and a question of whether there were special problems in reaching consensus in Europe as opposed to the U.S. (There is none of the "normative" litigation in Europe that we have here to bring about homogeneous standards.) To a man, the CRM felt that politicians made all the final technical decisions concerning health practice (payment) and that the CRM was merely advisory and rather powerless. I advised sticking to scientific/technical facts, avoiding opinions, and standing adamant against political values in their own recommendations.

I conveyed to the CRM the wish of our sister agency ADAMHA, especially NIDA, for an opportunity to have collaboration with CRM member nations in collecting epidemiological information concerning narcotic addiction, particularly serious side effects of overdosage. The response was positive and Dr. Donato indicated they would give consideration to working with NIDA.

I outlined the present Recombinant DNA guidelines in the U.S. and went into the question of mandatory rules vs. voluntary compliance. For some time, the CRM has not been active in offering advice on this subject. From Van Hoeck, I obtained a copy of the draft directive, developed in August 1978 by the Directorate-Generale for Research, Science and Education. This

is a proposal to CREST, suggesting it pass a directive (having binding force on member countries) "compelling the Member States to adopt general precautions against hazards possibly associated to certain forms of recombinant DNA work."

After a fair discussion of the background, the proposaal comes on strong for a "necessity for national laws on the matter." The arguments include:

- gravity of the hazards: "If the gravity of the risk involved in such as to require the elaboration of these expensive protection devices (physical and biological containment) it certainly justifies the preparation of orders intended to insure that they effectively serve their purpose. . . ."
- expansion of recombinant work: " . . . Thus risk, if there is one, . . . is increasing with time in proportion to the total number of sites. . . ."
- transnational nature of the risks: Lack of barriers at national borders (means) " . . . agreement must be reached within communities of neighboring countries on . . . general objectives and scale of the protection systems . . . and guarantees must be given to the respect of these agreements . . . through legal dispositions, taken in each country . . . based on a core of principles adopted in common."
- research in laboratories from private enterprises: notes intolerable nature of all not observing same rules creates something other than a voluntary system, it is " . . . equally obvious, in view of the importance of recombinant DNA technology for the promotion of European bio-industries, that . . . legislation . . . must not endanger intellectual property rights . . . and (must minimize) the disclosure of confidential scientific information."
- harmony between member states: requires national legislations, harmonized by community principles to avoid " . . . concentration of research activities in the most permissive states."

- the exemplary value of legislation on recombinant DNA technology: Recombinant DNA " . . . constitutes . . . choice material for establishing compatibilities between legislation and the development of modern technologies and for preparing a first basis to . . . (future such) dispositions The opportunity should not be missed."

The draft Directive accompanying the analysis:

- 1) requires prior notification and (except for activities falling in categories of low risk) prior authorization for all recombinant work;
- 2) leaves to the Member States the categorization and containment assignments;
- 3) specifies registration and general requirements;
- 4) encourages on-site examinations;
- 5) lays out some procedural requirements on each national authority, including, viz., decisions within 90 days, provision to detect and sanction against, breaches; and
- 6) Member States are required to keep the Commission informed on their rules and activities.

It was the CRM's opinion that the Director-General for Research, Science and Education intended to push the acceptance of this directive.

It was, therefore, of great interest to have the opportunity to chat with Dr. Gunter Schuster himself that afternoon. He had returned two hours earlier from India, but was fit and vigorous when we met at 2:30 p.m. We exchanged apologies, he for missing our luncheon, and I for forcing him to return to his office. We were each interested in meeting, however, and came quickly to pleasant and informative discussion. Schuster inquired of my views as to mandatory compliance. I told him of my continuing desire for uniform rules and observance, of my earlier desire for a simple national statute requiring the same, and my disappointment at the seeming impossibility of obtaining a law unencumbered by excesses of procedure and penalties. I informed him of Senator Stevenson's interest in a possible rule for mandatory notification. In sum, I preferred a simple rule, but chose voluntarism to inflexible regulation. We also discussed our recent decisions on changing the guidelines, including the provision for voluntary compliance and the range of reaction to it. He was grateful for a copy of the Federal Register release. At the end of our conversation, I had a distinct

impression that the Director General was to seek something less than a directive, perhaps rather, a recommendation of the Council. I am certain it was not our conversation alone, but a sense of the probabilities of passage of a mandatory directive, that was leading his opinions in this direction. Dr. Schuster and I agreed to stay in communication. His address is:

Dr. Gunter Schuster
Director General for Research,
Science and Education
Rue de la Loi, 200
1049 Brussels
tel:

In the evening, we flew to Paris and met with Dr. Philippe Laudat, Director of INSERM. Dr. Laudat indicated that the budget for INSERM was increased in the fiscal year to begin in January. It was his impression that European biomedical research support would "move ahead" of the support in the U.S. this year. (Our FIC study not being complete, I'm not sure that the available information base permits any conclusion about absolute support levels, but relative shifts in emphasis toward greater European support may be occurring.)

In the morning, we flew to London and were met at Heathrow by Sir William Henderson, Chairman of the British GMAG, and Dr. Keith Gibson, the MRC staff man for GMAG. When the luggage was at last retrieved, there being a slow-down of baggage handlers, we were driven to the Skyway Hotel where GMAG had prepared a small conference room for a consultation meeting.

In attendance were:

Sir William Henderson, Chairman, GMAG
Keith Gibson, MRC staff to GMAG
Dr. Wilke, MRC staff to GMAG
Dr. Dick Norton, Ministry of Education and Science (MES)
Dr. Herbert, Ministry of Education and Science (MES)
Dr. Donald S. Fredrickson, NIH
Dr. Joseph Quinn, NIH

The GMAG agenda for this meeting took the following course:

1) Scale-Up Decisions (including commercial confidentiality)

It appears that GMAG, which meets every six weeks, has been presented with 3-4 scale-up decisions for consideration. Only a few of these are for "use" (vis-a-vis, research), but commercial development is clearly proceeding in Britain. Of interest is a 4000 liter request from Distillation Products (for E. A. Lilly and insulin production). Confidentiality is maintained under

the Official Secrets Act. All participate except one T.U.C. representative, who is a hold-out on the pledge--no commercial consultant may participate, however, and GMAG is a bit thin in membership on such decisions. They have adopted a rule of no decision without a site visit. We explained that we do not automatically have participation by consultants, and do not require prior site visits. (We will be sending to GMAG some new rules we are promulgating on containment and scale-up.)

2) The U.S. EK1/Pl reduction proposal

We provided them with Federal Register decision prints one week old and answered questions concerning the decisions. Regarding the "Voluntary provision," we discussed possible Congressional Actions, industry responses so far, and the visit with Dr. Schuster in Brussels. GMAG does not desire the EEC directive, because of its conditions--90 day responses, and probably its constraints on both secrecy and independent action.

3) Risk Assessment Meeting in U.S. in March

The GMAG wishes to be represented. We indicated we wanted them to be there and that they would receive both an invitation and offer to suggest agenda items. The M.E.S. representative said one GMAG representative would be supported. (On return, I asked Dr. Krause to extend an invitation to GMAG.) I indicated Japan and other countries would be participating.

4) Future Location of GMAG

Both T.U.C. and C.B.I. (British industries) want GMAG to be a creature of the Health and Safety Executive rather than the Ministry of Education and Science. The former desires it because it wants stringent regulation, the latter because it wants no trifling with confidentiality. M.E.S. opposes any change, as does MRC and the Chairman. The Minister of the MES (Mr. Carlyle) and the Permanent Secretary (Neil McFarlane) oppose the switch. Of recent note is the suit brought against Birmingham University on a smallpox case (charge due to defective containment practice); courts have found against H/S and for the defendant. This is a failed test of H/S authorities.

- 5) GMAG membership -- 2 year changes:
- | | |
|---------------------------------------|---|
| Chairman | |
| Science and Medical Experts | 8 |
| Public Interest | 4 |
| Employees (TUC) | 4 |
| Management: | 2 |
| Vice Chancellor | |
| CBI representative | |
| + assessors from concerned | |
| departments: | |
| Agriculture, H/S, Scotland, HTSS, E/S | |

GMAG procedures: All decisions are by consensus. The British are generally appalled by voting in such advisories.

ESF/GMAG -- Meeting in January to be attended by Dr. Gartland. German law proposal on agenda.

We agreed to keep each other informed on GMAG/RAC actions, including proposal H/V exemptions or acceptances. We will use TELEX communication. GMAG offered liaison with RAC. (I prefer not to react to the suggestion at this time). Communications are at least free and mutual understanding is very high at present. Clearly, the new commercial exploitation makes harmony of rules essential.

This was a most valuable visit, especially considering its brevity.

DSF

THE SHANNON LEGACY AND MEDICAL RESEARCH TODAY*

*Donald S. Fredrickson, M.D.
Director, National Institutes of Health*

Any doubt that this is America's century in medicine will surely be dispelled when its history is written. This is largely attributable to the quality of the medical science that has developed in this country since the century opened. Early benchmarks on that ascending curve would surely include the formation of a clinical research unit at Johns Hopkins in about 1900—the first such unit that I know of anywhere. Others would be the opening of the Rockefeller Hospital in 1910, augmenting the already thriving Institute for Medical Research; and, at about the same time, the influence of American clinical research in Great Britain. Still another important development was the transformation and expansion of the present National Institutes of Health (NIH) out of what had been a small in-house laboratory for the Public Health Service. Many have contributed to that latter achievement; probably no single figure stands out more prominently than James A. Shannon.

In 1968 Dr. Shannon retired from another position, this time as the eighth director of NIH. His tenure of thirteen years was the longest in the history of that demanding position. When, in 1975, I succeeded him in this chair, the NIH he had left and the NIH I would now head were not so different. But the world in which it operated had changed greatly in seven years. The end of the 1960s had seen the trial and torment of elite institutions of all kinds, and science was not spared. The ethical frames in which we had to perform were shifting. There was a prescriptive element to the political economy surrounding medicine and its scientific base. A major source of anxiety was the rate of rise in the cost of health care, and some felt certain that science must be partly to blame.

There was, too, a sudden expansion in the power of experimental biology, which gave rise to anxieties of another kind. I began to engage in some problems that Jim Shannon would

Editorial notes:

*Delivered at 50th Anniversary Symposium of Blue Cross/Blue Shield Association, Wash., D.C., December 12, 1979.

Published in Working for a Healthier America, W. J. McNerney (Ed.), Ballinger, Cambridge, 1980, pp. 247-250.

have found strongly antitraditional. For one, I acquired the task of promulgating guidelines for the conduct of genetic engineering in terms of the techniques for using recombinant DNA. About 40 percent of my time in my first two years was devoted to coping with the confrontation between some anxious critics and a concerned but angry segment of the scientific community. Each was suspicious of the other, and yet they were trying to draw together—to close the gap of perception between the laity and the scientists and among many scientists themselves.

I also surveyed worriedly the boundaries of NIH, lines whose shape also fixed the azimuth of medical science in America. I was concerned, particularly, with what was, and what was not, appropriate for an organization whose objectivity was crucial and whose resources, although great, were always less than the sum of congressional expectations for scientific solutions. We had to seize some appropriate roles in resolving the suspicions and social problems that had sprung from modern biomedical technology. We had to restore confidence in the ability of our science to address practical problems. As one response, we began the technology assessment exercises—the “searches for consensus,” carefully programmed analyses of the state of the art that have recently made NIH much more of a household word to physicians than heretofore.

Third, we engaged in activities that I think Jim Shannon would also have viewed with bemusement. We have sat for many hours with all the sister agencies of the Public Health Service in an ecumenical effort to get the health sciences in the Department of Health and Human Services to recognize certain common principles for federal funding in the future. We looked at questions that have become increasingly nagging over three or four years. None of the cries is more demanding than those of the regulatory agencies seeking instant knowledge to help them to meet their mandates for regulation. In addition, there are the rising questions of whether we can improve and expand health services research and perform more clinical trials to refine better the substance of medical practice today and to assist in setting some limits to the growth of its cost. Such health research planning—the straining for a global perspective—has not been all comfortable. Yet we have begun

to address the complementarity of the agencies in ways that both improve the federal presence in health as well as leave its research arm free of activities inappropriate for medical science.

There are signs of progress. The new National Center for Health Care Technology, an HHS institution, will take up some of the most value-laden questions about new and old inventions that make up the fabric of health care. NIH can be properly concerned with only the technical and scientific questions here.

We are approaching a point in the evolution of NIH guidelines for DNA research that establishes them as the primary standard for the world, and in ways that now see the technology expanding and flourishing without excessive regulation and cumbersome statutory restriction.

In fostering certain special programs that relate us to the regulatory agencies, like the National Toxicology Program, we have gainsaid a great deal of the criticism that we were indifferent to the practical needs of the regulatory agencies. Thus we can enhance their search for standards, join them to the cutting edge of scientific advance, and avoid our participating directly in regulatory activities.

I think, too, that we are beginning to see the emergence of several agencies, notably the Center for Disease Control in the Public Health Service, with a stronger role in health promotion, again making it possible for the boundaries of NIH to be drawn in such a way that we can avoid placing our objectivity in peril by excessive peddling of the inventions emerging from science.

To me, these were the most important tasks of the last five years—crucial hurdles to mount in order that we might get on to some of the other issues raised by Dr. Shannon. There is no question in my mind that the power of biological and medical science today is greater than it was when I came to NIH. For example, there is the extraordinary capability that we now have in molecular biology. I am sure that it will eventually be possible to make in bacteria virtually any product of human genes. This will create cheaper and purer supplies of hormones, other biologicals, and monovalent vaccines against a whole variety of agents. We may even be able to control the

instability of the influenza virus in a practical way to make better live vaccines. There is no foreseeable limit to the future of medical science in better serving the preventive and curative practices in American medicine.

Clinical trials will continue. They impose a special burden, but our ability to perform them well certainly reflects the developments that occurred when Jim Shannon was trustee of the nation's medical research apparatus.

I think we have now begun to cope with another major problem—stabilization of the support for science in this country. And I speak not only of fundamental science, but of clinical science as well. With the growth of NIH, a social contract came into being in America. It is not derived from natural law, but from a sense of opportunity for scientists and the public to do a job together in using human creativity in the most humane and useful ways. We must find in the 1980s ways to insure the exceedingly close relationship between fundamental work in the life sciences and the constant movement of the findings toward practical use in society. The basic and the applied efforts do lie at opposite ends of a spectrum, and their social support and economic underpinning do derive, as Dr. Shannon has pointed out, from different sentiments. Yet, if I argue that the isolation of basic from applied research would split the continuum of medical science, it is not to deny serious problems within the educational institutions where most of the research goes on. Furthermore, it is apparent that the universities and the government do not understand each other well. Charges that regulations and procedures are stifling research, on the one hand, and of fraud and lack of accountability for public money, on the other, are symptoms of disorder for which simple prescriptions are not available. Speaking for the NIH of Dr. Shannon and his successors, I know that we shall commit much of our time and energies in the coming year to understanding and relieving some of the distress that he perceives.

OPENING REMARKS BY DR. DONALD S. FREDRICKSON

Dr. Martin Luther King, Jr., Commemorative ProgramJanuary 15, 1980

On behalf of all of my co-workers at the National Institutes of Health, it is my pleasure and privilege to welcome our distinguished guests who have come to join with us in a special time of remembrance and rededication.

In celebrating the birthday of Dr. Martin Luther King, Jr., we bear witness to the incredible power of the human spirit. His short life set in motion waves of influence that have swept around the world touching and moving millions who are determined to continue his works until all are truly free.

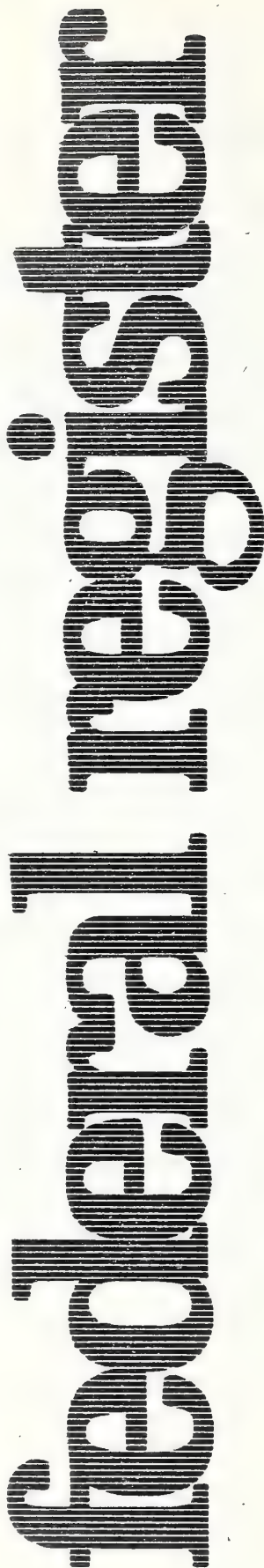
We are honored indeed to have with us today his daughter, Ms. Yolanda King, and the Honorable Parren Mitchell, a respected and influential member of the Congress of the United States.

Ms. King and Congressman Mitchell will be formally introduced later in the program - as will the talented singers and dancers whose presentations will speak in their unique way to our minds and hearts.

We celebrate the birthday of Martin Luther King, Jr., in gratitude for the meaning of his life, the challenges and the hopes he left us.

#

Tuesday
January 29, 1980



Part V

**Department of
Health, Education,
and Welfare**

National Institutes of Health

**Recombinant DNA Research; Actions
Under Guidelines**

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

Recombinant DNA Research; Actions Under Guidelines

AGENCY: National Institutes of Health, PHS, HEW.

ACTION: Notice of actions under NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: This notice sets forth actions taken by the Director, NIH, under the 1978 NIH Guidelines for Research Involving Recombinant DNA Molecules (43 FR 60108). Revised NIH Guidelines are printed following this notice.

EFFECTIVE DATE: January 29, 1980.

FOR FURTHER INFORMATION CONTACT:

Additional information can be obtained from Dr. William J. Gartland, Office of Recombinant DNA Activities (ORDA), National Institutes of Health, Bethesda, Maryland 20205. (301) 496-6051.

SUPPLEMENTARY INFORMATION: I am promulgating today revised NIH Guidelines for Research Involving Recombinant DNA Molecules. This announcement is a "Decision Document" explaining the background and reasons for my decision. Immediately following this announcement there appears a copy of the revised NIH Guidelines.

The structure of this Decision Document is as follows:

- I. History of the NIH Guidelines Through 1978.
- II. Revision of the December 1978 Guidelines.
- III. Analysis of Comments on Decision Document/Environmental Impact Assessment/Proposed Revised Guidelines as Published For Comment in the Federal Register on November 30, 1979 (44 FR 69210).

I. History of the NIH Guidelines Through 1978

The history leading to the issuance of the original 1976 NIH Guidelines for Recombinant DNA Research is described in detail in the Environmental Impact Statement on the 1976 Guidelines, and in the "Decision Document" accompanying the Guidelines in the Federal Register of July 7, 1976. Key points in the history included:

- The Maxine Singer-Dieter Soll letter (*Science* 181, 1114, 1973) arising from the Gordon Research Conference on Nucleic Acids of July 1973.
- The Paul Berg et al. letter to *Science* (185, 303, 1974) calling for the NIH to establish an advisory committee to write guidelines.

- The Asilomar conference of February 1975.
 - The work of the NIH Recombinant DNA Advisory Committee (RAC) through 1975, resulting in the proposed guidelines of December 1975.
 - The special meeting of the Advisory Committee to the Director, NIH, on February 9-10, 1976, to review the proposed guidelines.
 - Final issuance of the NIH Guidelines on June 23, 1976 (published in the Federal Register on July 7, 1976).
- The history from the period July 1976 to December 1978 included the following key points:
- Deliberations on revisions by the RAC during 1977, resulting in proposed revisions published for comment in the Federal Register on September 27, 1977 (42 FR 49596).
 - A public hearing on the revisions, at the meeting of the Advisory Committee to the Director, NIH, December 15-16, 1977.
 - Publication for public comment in the Federal Register on July 28, 1978 (43 FR 33042), of new proposed revised guidelines accompanied by a detailed Decision Document and a detailed Environmental Impact Assessment.
 - A public hearing on the proposed revisions, chaired by the General Counsel of HEW, on September 15, 1978.
 - Publication of revised guidelines on December 22, 1978 (43 FR 60080), accompanied by a detailed Decision Document and Environmental Impact Assessment.

The entire history is extensively documented in Volumes 1-4 of "Recombinant DNA Research"—a series constituting a readily available public record of activities in regard to the NIH Guidelines.

II. Revision of the December 1978 Guidelines

The December 1978 NIH Guidelines for Research Involving Recombinant DNA Molecules (43 FR 60108) include procedures for changing the Guidelines. As detailed in Section IV-E-1-b-(1) of the Guidelines, this involves: (1) publication in the Federal Register for public comment, at least 30 days prior to a RAC meeting, of the proposed changes; (2) consideration of the proposed changes by the RAC; and (3) publication in the Federal Register of the final decision by the Director, NIH.

In accordance with these procedures, proposed changes in the Guidelines appeared in the Federal Register on January 15, 1979 (44 FR 3226), were considered by the RAC at its February 16-17, 1979, meeting, and were promulgated by the NIH Director in the

Federal Register on April 11, 1979 (44 FR 21730).

Proposed changes in the Guidelines appeared in the Federal Register on April 13, 1979 (44 FR 22314), were considered by the RAC at its May 21-23, 1979, meeting, and were promulgated by the NIH Director in the Federal Register on July 20, 1979 (44 FR 42914).

Proposed changes in the Guidelines appeared in the Federal Register on July 31, 1979 (44 FR 45088) and were considered by the RAC at its September 6-7, 1979, meeting. Rather than promulgating the recommended changes, the Director, NIH, instead issued them for 30 days of additional public comment in the Federal Register on November 30, 1979 (44 FR 69210).

This was in accordance with Section IV-E-1-b-(1) of the NIH Guidelines (43 FR 60126) which says, "The Director's proposed decision, at his discretion, may be published in the Federal Register for 30 days of comment before final action is taken." What appeared in the Federal Register on November 30 was a detailed "Decision Document" explaining the background and reasons for the proposed decision, an Environmental Impact Assessment, and proposed revised NIH Guidelines. Included was an analysis of many letters received prior to November 30. Part III of the present document contains an analysis by the Director, NIH, of all comments received during the period November 30, 1979 to January 18, 1980 on the Decision Document/Environmental Impact Assessment/Proposed Revised Guidelines as published in the Federal Register on November 30, 1979. All of the changes in the Guidelines accepted by the Director, NIH, and promulgated today have been found by the Director, NIH, in accordance with Section IV-E-1-b of the NIH Guidelines, to comply with the Guidelines and to present no significant risk to health or the environment.

Proposed changes in the Guidelines appeared in the Federal Register on November 1, 1979 (44 FR 63074), were considered by the RAC at its December 6-7, 1979, meeting, and were promulgated by the NIH Director in the Federal Register on January 17, 1980 (45 FR 3552).

Immediately following this "Decision Document," there appears a copy of the revised NIH Guidelines which are effective today. These were obtained by incorporating into the December 1978 Guidelines all the changes made following the February 16-17, 1979, May 21-23, 1979, September 6-7, 1979, and December 6-7, 1979, RAC meetings.

III. Analysis of Comments on Decision Document/Environmental Impact Assessment/Proposed Revised Guidelines as Published for Comment in the Federal Register on November 30, 1979 (44 FR 69210)

III-A. Discussion at RAC Meeting on December 6, 1979

The Decision Document/Environmental Impact Assessment/Proposed Revised Guidelines as sent to the Federal Register to appear on November 30, 1979, were simultaneously sent to RAC members who received the documents on November 29. The material was discussed by the RAC at its December 6-7, 1979, meeting. At this meeting, the RAC Chairman presented the document pointing out the changes between the "E. coli K-12/P1 Recommendation" as adopted by the RAC on September 6, 1979, and the somewhat revised version of this recommendation (Section III-O of the proposed revised Guidelines) as issued by the NIH Director for public comment in the Federal Register on November 30, 1979. She noted that the NIH Director had eliminated the reference to these experiments as "exempt from the Guidelines" and had added a requirement for prior review and approval by the IBC for experiments in which there is a deliberate attempt to have the *E. coli* K-12 efficiently express a gene coding for a eukaryotic protein. The Chairman asked for comments from the RAC. Except for questions of clarification from RAC members, which were answered by NIH staff, there were no comments either on these particular items or on the recommendations generally. NIH staff urged RAC members to write individually to the NIH Director during the comment period giving their views. (Six RAC members did write. Four endorsed Section III-O of the Guidelines. Two, who had voted against the "E. coli K-12/P1 Recommendation" at the September 6-7, 1979, meeting, wrote. One urged the "exemption" not be approved. The other urged that the final decision not be delayed.)

III-B. Public Comments

The Decision Document/Environmental Impact Assessment/Proposed Revised Guidelines as they appeared in the Federal Register on November 30, 1979, were sent out to over 2000 people for comment—this included the chairmen of all Institutional Biosafety Committees registered with NIH, all principal investigators doing recombinant DNA experiments supported by NIH, and all persons who had previously requested their inclusion

on a mailing list to receive information concerning the NIH Guidelines. During the period up to January 18, 1980, 185 letters signed by a total of 205 individuals were received. All of these letters: (i) are now available for public inspection at ORDA; (ii) can be made available (in whole or in part) to any requester upon payment of reproduction costs; and (iii) will be published (and subsequently may be purchased through the U.S. Government Printing Office) as part of Volume 5 of "Recombinant DNA Research," a series constituting a public record of activities in regard to the NIH Guidelines.

The Decision Document/Environmental Impact Assessment consisted of an analysis of the six "major actions" which were recommended favorably at the September 6-7, 1979, RAC meeting. These six "major actions" were: "The *E. coli* K-12/P1 Recommendation"; "Proposed Amendment of Sections II-D-1-a-(1) and III-A-1-b-(1) of the Guidelines"; "Proposed Exemption for *Pseudomonas Putida* and *Pseudomonas Florescens*"; "Cloning in *Bacillus Subtilis* and *Streptomyces Coelicolor*"; "Use of *Agrobacterium Tumefaciens* as a Host-Vector System"; and "Proposed Supplement (Part VI) to the Guidelines."

The bulk of the November 30 Decision Document/Environmental Impact Assessment consisted of an analysis of the "E. coli K-12/P1 Recommendation"; it was pointed out that "of all the recommendations arising from the last three meetings of the RAC [this recommendation was] the one that has generated the greatest number of letters and the most discussion at the RAC meetings." The analysis included the NIH Director's proposed acceptance of a modified version of this recommendation to become Section III-O of the proposed revised Guidelines.

In the comment period only three letters were received that included comments dealing specifically with any of the other five "major actions" i.e., all other letters made reference to the entire proposed revised Guidelines or commented specifically upon the "E. coli K-12/P1 Recommendation." The remainder of this document is organized as follows: III-B-1. Comments on The Entire Proposed Revised Guidelines; III-B-2. Comments on the "E. coli K-12/P1 Recommendation" or Section III-O of the Proposed Revised Guidelines; III-B-3. Comments on the Proposed Revised Guidelines Other Than Section III-O; III-B-4. Comments on the Guidelines Other Than Changes Recommended by the RAC; III-C. Decision of the NIH

Director on Promulgation of Revised Guidelines.

III-B-1. Comments on the Entire Proposed Revised Guidelines

Eighty-three letters signed by a total of 100 individuals were received in support of the proposed revised Guidelines. (Many of these commentators also specifically endorsed Section III-O of the proposed Guidelines.) Comments included the following—"I heartily support the changes that you propose for the NIH Guidelines for Research Involving Recombinant DNA Molecules. I am especially impressed by the detailed and reasoned consideration that the Advisory Committee (RAC) and you have used to reach these very enlightened decisions."—"This letter is to indicate my wholehearted support of the revisions."—"Although I am highly concerned with laboratory safety, I believe the revised guidelines are certainly reasonable."—"They are reasonable and sensible Guidelines which take into account the body of new information and research experience which has become available since the formulation and enactment of the original guidelines."—"The proposed new Guidelines are a very sensible step forward. By freeing scientists from unnecessary red tape, and administrative delays in doing experiments, they will appreciably accelerate the progress of research and the realization of its benefits."

III-B-2. Comments on the "E. coli K-12/P1 Recommendation" or Section III-O of the Proposed Revised Guidelines

Comments received on the RAC's "E. coli K-12/P1 Recommendation" or the NIH Director's proposed incorporation of a modified version of this recommendation to become Section III-O of the proposed revised Guidelines are discussed below.

III-B-2-a. Endorsement of the "E. coli K-12/P1 Recommendation" or Section III-O of the Proposed Revised Guidelines

In addition to the 83 letters mentioned above which endorsed the entire proposed revised Guidelines, another 86 letters signed by a total of 89 individuals were received endorsing what was referred to as either the proposed new "Section III-O of the Guidelines," the "E. coli K-12/P1 Recommendation," or the "decision to reclassify recombinant DNA experiments performed in *E. coli* K-12 as P1." Thus, of the 185 letters received, 169 supported the proposed new Section III-O.

These commentators included four RAC members, and six former RAC members. Comments included the following—"Section III-O describing experiments with *E. coli* K-12 host-vector systems represents a realistic and safe modification of some of the previous regulations. . . . We wish to express our confidence in the good judgment and scientific qualifications of the committee that has made these decisions. The enormous effort in preparing these guidelines in the interest of all of us should earn high praise."—"In Section III-O there is a classificatory downgrading of a large group of experiments in *E. coli* K-12. I applaud that change. It appears to me to be soundly based on the accumulating experience and evaluation of real hazards of such experiments."—"For this reason, I strongly endorse the decentralization of control over experiments using the *E. coli* K-12 Host-Vector systems as outlined in section III-O."—"I, therefore, urge adoption of Section III-O, as a way of eliminating a costly and time-consuming unnecessary obstacle to research of great practical importance as well as scientific interest."—"In particular, I specifically endorse the revision of the guidelines concerning the K-12 containment (section III-O). The proposals are a reasonable way of matching the realistic risks with the clear benefit of removing unnecessary administrative work."—"I believe that the category change is fully consistent with public safety, and is essential to permit legitimate health related research dependent upon cloning techniques to proceed."—"I consider the evidence overwhelming that these experiments pose no significant hazard."

III-B-2-b. Request that Experiments Involving E. coli K-12 Be Exempted from the Guidelines

Nine commentators, while indicating their endorsement of Section III-O, also indicated that they favored a somewhat greater relaxation of the Guidelines. Comments included the following—"My personal opinion is that the data does not even warrant registration of these experiments."—"My current view is that even P1 containment is probably unnecessary."

Nineteen commentators wrote requesting that all or most experiments with *E. coli* K-12 be completely exempted from the Guidelines; this would relax the conditions for doing these experiments much further than I had proposed in Section III-O of the proposed revised Guidelines. (Some of these commentators endorsed Section III-O as a "step in the right direction.") Comments included the following—"To

continue Federal regulation after evidence has been obtained that there is no clear threat to the public health is a waste of already dwindling Federal scientific resources and in addition, sets an ominous precedent for future Federal regulatory adventures. In addition, at the level of the working scientist or student, the perpetration of needless regulations, directed at imagined hazards, undercuts our continuing efforts to institute and make effective safety practices governing the handling of real pathogens and toxic agents."

On the other hand, four commentators specifically endorsed the decision that experiments with *E. coli* K-12 not be exempted from the Guidelines, and four commentators specifically endorsed IBC registration of these experiments.

In my Decision Document/Environmental Impact Assessment of November 30, 1979, I discussed why I was not proposing to exempt from the Guidelines experiments under the "*E. coli* K-12/P1 Recommendation." As I wrote then, and still believe is prudent policy: "Three important safety features for these experiments that will not be exempt, but will according to the proposed decision form a special class under the Guidelines, are:

"1. P1. Containment—Including the ban on mouth pipetting and the requirement that all biological wastes shall be decontaminated. Proper employment of P1 conditions eliminates the primary means of *E. coli* escape from the laboratory.

"2. EK1—Allowing only *E. coli* K-12 strains and not allowing the use of conjugation proficient plasmids or generalize transducing phages. This greatly reduces the probability that any escaping *E. coli* K-12 would survive and transfer their recombinant DNA to other organisms.

"3. IBC Oversight—Continuing local surveillance and registration of these experiments.

"In addition, keeping these experiments under the Guidelines rather than exempting them means that any scale-up of the experiments beyond 10 liters will require prior NIH approval."

These important safety features apply to the experiments described in Section III-O of the proposed revised Guidelines; they would not apply if these experiments were exempted from the Guidelines.

III-B-2-c. Request That Section III-O of the Guidelines Not Be Promulgated

Of the 185 letters received by January 18, 1980, five said that Section III-O and/or the proposed revised Guidelines should not be promulgated. These five commentators included one current and

one former RAC member. Among the comments they made were:

1. "I urge you to extend the comment period."

2. The NIH Director should reconsider "the *E. coli* exemption as voted for by the RAC at its September 1979 meeting."

3. "It needs emphasis that there is currently no requirement (only a recommendation) that institutions require workers in this field to be trained in good laboratory practice."

4. Many of the arguments used to justify this revision of the Guidelines were used to justify a previous revision.

5. The discussion in the November 30 Decision Document "implies that microorganisms do not 'escape' from laboratories in which containment is supposed to be practiced."

6. "I continue to be disturbed that such far-reaching policy changes are being considered in the absence of data from a risk-assessment program."

7. "I'm less than totally convinced by the information in the November 30, 1979 Federal Register that it is prudent to allow cloning of all DNA at the P1 + EK1 level except where prohibited."

None of these commentators provided any new scientific data.

In reply to the first comment given above, I note that although the comment period formally ended December 30, 1979, I considered all letters received until January 18, 1980.

In response to the second comment given above, I note that the November 30 Decision Document/Environmental Impact Assessment discussed in detail why I am not in fact exempting these experiments from the Guidelines.

In response to the third comment given above, the NIH Guidelines do in fact require training of workers. Section IV-D-1-g of the Guidelines discussing responsibilities of the Institution says the Institution shall "Ensure appropriate training for the IBC chairperson and members, the BSO, Principal Investigators (PIs), and laboratory staff regarding the Guidelines, their implementation, and laboratory safety. Responsibility for training IBC members may be carried out through the IBC chairperson. Responsibility for training laboratory staff may be carried out through the PI. The Institution is responsible for seeing that the PI has sufficient training, but may delegate this responsibility to the IBC." Section IV-D-3-a-2 says the Institutional Biosafety Committee is responsible for "An assessment of the facilities, procedures, and practices, and of the training and expertise of recombinant DNA personnel." Section IV-D-5-d-2 of the Guidelines says the Principal Investigator is responsible for

"Instructing and training staff in the practices and techniques required to ensure safety and in the procedures for dealing with accidents."

In response to the fourth comment given above, I note that this was discussed in the November 30 Decision Document/Environmental Impact Assessment under the consideration of the comments "Data Are Not Sufficient To Justify Exemption."

In response to the fifth comment given above, we did not mean to imply that microorganisms do not escape from laboratories in which containment is practiced. Data on laboratory-acquired infection rates at different physical containment levels were given in the NIH Environmental Impact Statement on the 1976 Guidelines where it was pointed out that "when known hazardous agents are handled, the risk of a laboratory-acquired infection cannot be totally eliminated." What is discussed in the November 30, 1979, Decision Document/Environmental Impact Assessment is the low probability of *E. coli* K-12 escaping in significant numbers from a P1 laboratory. This, combined with the low probabilities of a series of other steps discussed in that document, leads to an extremely low probability of hazard arising from *E. coli* K-12 carrying recombinant DNA.

In response to the sixth and seventh comments given above that changes are being made "in the absence of data from a risk-assessment program," or upon insufficient data, I must note that the November 30 Decision Document/Environmental Impact Assessment discussed in detail the substantial body of data available on the safety of *E. coli* K-12 and specifically dealt with the issue of risk-assessment under the discussions of the comments "Delay Any Change in the NIH Guidelines Pending Many More Risk-Assessment Experiments," and "Data Are Not Sufficient to Justify Exemption" as well as the alternative "Make No Change In The Guidelines Until Many More Risk-Assessment Experiments Are Completed." I continue to believe, as I wrote then, that the action is fully supported by the data.

III-B-2-d. Comments on the Time Taken To Promulgate the NIH Director's Decision on This Recommendation

Fourteen commentators, including one of the four RAC members who voted against the "*E. coli* K-12/P1 Recommendation" at the September 6, 1979, RAC meeting, wrote against delay, noting that the RAC's "*E. coli* K-12/P1 Recommendation" had been made in September 1979 but not yet promulgated.

Comments included the following—"It is regrettable that these revisions have been delayed for further comment in view of the extensive period provided already for such comments and the extensive discussions by the Recombinant DNA Advisory Committee prior to its votes. I believe that the expense in terms of time taken from other fruitful activities of yourself and the many commentators on this issue was unnecessary and extremely wasteful."—"I am appalled at the interminable delays required before a recommendation of the RAC can be put into effect. The procedures required by the December 1978 guidelines are cumbersome enough without an additional layer of public comment, analysis, and justification added on. NIH and American biomedical scientists deserve better treatment and trust from their top health administrators."—"It is disheartening to find that, even after thorough consideration and approval by RAC, the *E. coli* K-12/P1 measure remains in administrative limbo."—"The unnecessarily long delays in implementing the new guidelines have adversely affected the morale of American scientists and hampered progress in this highly significant area of research and development."

On the other hand, one commentator wrote, "I once again congratulate you on the exemplary way in which revision of these guidelines is being continued while still making proposals available to the public for scrutiny before their final adoption."

I am firmly committed to the procedures of the NIH Guidelines. As pointed out above in Section II of this document, procedures for revising the Guidelines involve certain mandatory "delays" including publication of the proposed changes in the Federal Register for public comment, at least 30 days prior to a meeting of the RAC, and consideration of the proposed changes at a formal RAC meeting. For recommendations arising from three of the last four RAC meetings, there was no additional public comment period. For the recommendations made at the September 6-7, 1979, RAC meeting, however, I did issue my proposed decision for an additional 30-day period of public comment. It is my intention, generally, in the future, to rely, in formulating my final decision, on the comments received in the initial comment period, and on the recommendations of the RAC, without issuing a proposed decision for an additional period of public comment.

III-B-2-e. Ff Bacteriophages

Three letters discussed the use of Ff bacteriophages. One wrote, "Nor can I see why other *E. coli* K-12 host-vector systems, such as those employing Ff bacteriophages, are not included within the Section III-O reduction." Another wrote, "I certainly hope that this proposal will be extended to the Ff bacteriophages in the near future."

I discussed this in detail in my November 30, 1979, Decision Document/Environmental Impact Assessment under the alternative "Include Ff Bacteriophages (Filamentous Single Strand Male Specific Bacteriophages such as M13 and fd) With Lambda or Lambdoid Bacteriophages To Be Permissible Under the '*E. coli* K-12/P1 Recommendation.'" There, I noted that I would "ask the RAC to consider the use of Ff bacteriophages again." At the December 1979 RAC meeting, a Working Group was appointed to consider this issue. They will report to the RAC at its next (March 1980) meeting. I will consider the recommendations of the RAC before taking action on inclusion of Ff bacteriophages within Section III-O.

III-B-2-f. Requirement for IBC Prior Review and Approval When There Is a Deliberate Attempt To Have the E. coli K-12 Efficiently Express a Gene Coding for a Eukaryotic Protein

One of the differences between the "*E. coli* K-12/P1 Recommendation" made by the RAC on September 6, 1979, and my proposed modification of this recommendation to become Section III-O of the November 30, 1979, proposed revised Guidelines was the addition of the text which states, "An exception, however, which does require prior review and approval by the IBC is any experiment in which there is a deliberate attempt to have the *E. coli* K-12 efficiently express any gene coding for a eukaryotic protein."

Four commentators wrote in opposition to this. One said that the requirement "is in my view superfluous, and is almost guaranteed to cause nuisance and confusion for investigators and IBC's. Many IBC's will understand this section to imply that they must require higher containment for such experiments, and for this the guidelines give no guidance or clarification. This requirement will expose many investigators to arbitrariness and unnecessary restrictions. . . . The Guidelines should clarify the intent of this requirement and should explicitly state that P1 containment is recommended. . . ." Two other commentators urged that this sentence be eliminated. One wrote, "Failing that

amendment, I must ask for a clarification of the intent of the sentence in question. As I read the relevant paragraph, these "expression" experiments are understood to be appropriately carried out at the P1 + EK1 level of containment. I am afraid that an alternate, presumably unintended, reading would be that each IBC is urged to set its own standards on these experiments. This policy, I am sure you would agree, would be disastrous."

On the other hand, three commentators wrote in favor.—"I agree with your decision to require that experiments in which there is a deliberate attempt to have expression of a eukaryotic gene be reviewed and approved by the local IBC prior to their being performed."

In response, I do not judge this requirement to be "superfluous." I discussed it in my November 30, 1979, Decision Document/Environmental Impact Assessment under the alternative "Treat Experiments Equally In Which There Is Or Is Not A Deliberate Attempt To Achieve Gene Expression." There, I concluded the discussion on this issue by stating, "Therefore, experiments in which there is a deliberate attempt to achieve gene expression continue to merit special attention. . . . This will allow the IBC to judge whether it wishes to require any added restrictions to be placed on the experiment, and to remain fully informed of its progress."

In response to the request that the Guidelines "should explicitly state that P1 containment is recommended," I note that the Guidelines do explicitly state in Section III-O that ". . . experiments using *E. coli* K-12 shall use P1 physical containment. . . ." including those "in which there is a deliberate attempt to have the *E. coli* K-12 efficiently express any gene coding for a eukaryotic protein. It is not NIH's intention that the IBC must require higher containment for such experiments."

One commentator suggested a rewording of this sentence as follows—"An exception, however, which does require prior review and approval by the IBC is any experiment in which there is a deliberate attempt to have the *E. coli* K-12 efficiently express as a protein product the information carried in any gene derived either from a eukaryotic organism or from any virus or viroid which infects a eukaryotic organism." I will have this suggestion published for at least 30 days public comment, and will ask the RAC to consider it at its next (March 1980) meeting before I take action on it.

III-B-2-g. Use of Poorly Mobilizable Plasmids

One commentator suggested that

experiments described in Section III-O of the Guidelines which specify that "the host shall not contain conjugation-proficient plasmids" add an additional safety feature by the use of "a poorly mobilizable plasmid. By that I mean one that is mobilizable at frequencies of $<10^{-5}$ by a derepressed conjugative plasmid." I will have this suggestion published for at least 30 days public comment and will ask that it be considered first by the RAC Subcommittee on Host-Plasmid Vector Systems, and then by the full RAC at its March 1980 meeting, before I take action on it.

III-B-2-h. Transfer of Clones to Other Laboratories

One correspondent discussed "the requirement that clones subject to the guidelines can be transferred to other laboratories only after the recipient submits an approved MUA to the supplying laboratory" and questioned whether this should apply to clones described in Section III-O of the Guidelines.

Detailed instructions on the administration of the NIH Guidelines are contained in the "Administrative Practices Supplement to the NIH Guidelines for Research Involving Recombinant DNA Molecules" (APS). Currently, a Memorandum of Understanding and Agreement (MUA) is required to be submitted to NIH for each NIH-funded recombinant DNA project subject to the Guidelines. As described in the APS, the MUA must contain a statement "agreeing to abide by the provisions of the NIH Guidelines and the requirements of this Supplement concerning shipment and transfer of recombinant DNA materials." The revised NIH Guidelines, issued today, specify that for experiments described in Section III-O, "no Memorandum of Understanding and Agreement (MUA) . . . need be submitted. . . ." NIH will soon issue a revised version of the APS taking into account the changes in the Guidelines promulgated today. At that time, requirements concerning shipment of clones described under Section III-O of the Guidelines will be described.

III-B-3. Comments on the Proposed Revised Guidelines Other Than Section III-O

Only three comments were received dealing with a "major action" recommended at the September 6-7, 1979, RAC meeting, other than the "*E. coli* K-12/P1 Recommendation." These three requested that the Proposed Supplement (Part VI) on Voluntary Compliance not be added to the Guidelines. The reason given by one commentator was that it may "lead to unnecessary and wasteful legislative

attempts." The other two commentators, on the other hand, specifically called for mandatory compliance.

In my November 30 Decision Document, I reviewed the history of this proposed supplement in detail including endorsement of it by the Federal Interagency Committee on Recombinant DNA Research and by the RAC. In accord with the analysis in that document, I accept the recommendation of these two committees to add Part VI to the Guidelines.

III-B-4. Comments on the Guidelines Other Than Changes Recommended by the RAC

The Decision Document/Environmental Impact Assessment/Proposed Revised Guidelines, as published for public comment on November 30, were based upon changes in the Guidelines recommended by the RAC at its September 6-7, 1979, meeting. During the comment period, five letters were received proposing additional changes in the Guidelines totally unrelated to the RAC recommendations. One commentator requested exemption from the Guidelines of "return to host of origin" type experiments. One commentator requested that the Institutional Biosafety Committee members not affiliated with the institution "shall be appointed by the governing body of the community in which the institution is situated." Two commentators submitted a proposed addition to Appendix B of the Guidelines to deal with plant pathogens. One commentator requested elimination of Prohibition I-D-3, and a revision of Sublist A of Appendix A to the Guidelines.

I will have the proposals mentioned above under III-B-4 published for at least 30 days public comment, and will ask the RAC to consider them at its next (March 1980) meeting before I take action on them.

III-C. Decision of the NIH Director on Promulgation of Revised Guidelines

Based on my analysis of the comments received during this comment period, I am today promulgating revised NIH Guidelines for Research Involving Recombinant DNA Molecules. They differ from the proposed revised Guidelines as published in the Federal Register on November 30, 1979, by the incorporation of the additional changes which were recommended by the RAC at its December 6-7, 1979, meeting, and which were promulgated in the Federal Register on January 7, 1980 (45 FR 3552).

Dated: January 23, 1980.

Donald S. Fredrickson,
Director, National Institutes of Health.

[FR Doc. 80-2821 Filed 1-28-80; 8:45 am]

BILLING CODE 4110-08-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

Statement by the Director

Mr. Chairman and Members of the Committee:

I welcome the opportunity today - my fifth as Director of the National Institutes of Health - to appear before the distinguished Chairman and members of this Committee to testify on behalf of the President's budget request for the National Institutes of Health. Both the preparation for these hearings, and the discussions generated by the Committee continue to be most helpful to me in carrying out my responsibilities during the rest of the year.

The importance of these hearings derives from two basic facts with which you are familiar: the NIH is the Nation's largest biomedical research institution, and it is also by far the largest single source of funds for biomedical research conducted in the universities, medical schools, and research institutions of this Nation. Together these activities will determine much of the quality of health care for tomorrow, and sustain the quality of health professional education today. Thus the total resources of the NIH translate quite directly into the Nation's capability and achievement in the health sciences. Although our country's leadership here is being challenged, we are still extremely powerful and influential in this area of human service.

Last year I described our efforts to set biomedical research priorities in line with budget constraints. This year a formal planning process was extended to the Department's entire health research budget to seek greater efficiency and cohesiveness in the conduct of health research.

One focus of the planning process implemented by this year's budget is the Administration's commitment to sustain one of the major activities aimed at enhancing the science base. An important part of such research is provided by investigator-initiated research project grants awarded by the National Institutes of Health. These have been selected for emphasis to signal the recognition of the Nation's intent to maintain fundamental research as an indispensable long-term societal investment. Proof of this intent is absolutely necessary to assure that young Americans will continue to make the sacrifices necessary to invest their careers in the health sciences.

The number of competing projects funded in a given year has the virtue of allowing us to predict the numbers of scientists who can count on this type of support. The ability of the NIH to fund about 5,000 competitive projects or about one-third of approved grant applications in 1981 testifies to the Administration's determination to protect the national commitment for this type of research from the erosion of inflation.

It would be inappropriate and inaccurate, however, to create the impression that support of investigator-initiated research project grants is the only critical demand that must be met in biomedical science. The government's intramural research programs offer indispensable, and sometimes unique forces in the quest for scientific

information relative to agency missions. Our own NIH intramural program serves as a benchmark of excellence for our Nation's biomedical research community.

Approximately 70 percent of the NIH staff are associated with research conducted in the laboratories and clinics of the National Institutes of Health. Recent evaluations of the intramural research program give clear indication that it provides a milieu for research productivity that is second to no other institutional form. There is no question that the assets of the intramural program at NIH: the scientists, their supporting co-workers, and the facilities at its several campuses, are invaluable and irreplaceable national resources.

As the Committee is well aware, the NIH Clinical Center is a unique institution. It is the Nation's, and the world's, largest hospital dedicated totally to research on the diseases of mankind. The Ambulatory Care Research Facility (ACRF) which will be integrated fully with the Clinical Center, and whose construction has been supported and funded by this Committee, is nearing completion.

The ACRF construction is accompanied by some essential modernization of the Clinical Center. I am pleased to report to you that for this modernization program the Buildings and Facilities appropriation request contains \$7 million in 1981 and a proposed \$7.23 million transfer in 1980 from the Institutes with programs in the Clinical Center. This is a part of a continuing effort begun in 1979 to integrate the Clinical Center with the new ACRF and to correct functional obsolescence and physical deterioration in the parent hospital facility. The 1981 budget also contains \$1.5 million for the initiation of a multiyear project to modernize other NIH laboratory

buildings which have been operational since the 1940's.

Various components of the new NIEHS facility are being completed and turned over to the Government. Our budget request for NIEHS contains \$5 million and 55 positions for support staff and equipment needed to operate its new facility in North Carolina.

Other biomedical research needs are reflected in this budget as well. Last year, with your support, NIH, for the first time in six years, increased its stipend levels for the National Research Service Award program. This budget provides a further modest but essential increase in these stipend levels to partially compensate for the effects of inflation.

We are also requesting \$1 million for an effort to attract promising minority high school students to careers in biomedical research. This program of short-term research experiences is a continuation of a program started in FY 1980 as part of the President's initiative to improve minority access to research careers.

Exciting advances are occurring across the full spectrum from fundamental research through clinical applications to the impact on health, care and prevention. Only three examples illustrate some of the far-reaching consequences:

Promise that greater control of the immune system may enable us to reduce or eliminate tissue destruction in such chronic diseases as arthritis.

Expectation that recombinant DNA technology will permit efficient manufacture of potent biological substances, such as insulin and interferon, and improve current vaccines.

Transfer to general medical practice the results of the recently

completed clinical hypertension trial conducted by the National Heart, Blood, and Lung Institute, revealing that treatment of mild hypertensives reduces rates of death and disability.

This year sees the fulfillment of the dream of former Senator Lister Hill that the National Library of Medicine enhance its information dissemination activities through the use of advanced technology. The completion of the Lister Hill Biomedical Research Communications Center will permit the National Library of Medicine to play this enhanced role.

The National Toxicology Program (NTP) has completed its first year and demonstrated it can join the research and regulatory agencies in common cause to determine toxicity of chemicals in the environment. NIH will increase its support for this program by \$20 million, largely through a redirection of funds, in the National Cancer Institute and by \$3 million in the National Institute of Environmental Health Sciences. With the increase, the NTP will begin 100 new bioassays for carcinogenicity, bringing the total at the end of the year to 320 bioassays in 1981 compared with 199 and 241, respectively, at the end of fiscal years 1979 and 1980.

The intramural programs of the NIEHS will be expanded by \$3 million in such areas as pathology, behavioral toxicology, and development of test procedures and risk assessment which are especially important to the National Toxicology Program.

Adjustments cannot be made in one portion of the research budget without correction for the balance of the rest. The time scale for appropriate adjustment is often longer than a single year. Although the primary focus in Fiscal Year 1981 is on extramural research

projects, activities such as clinical trials, research centers, demonstration programs and interdepartmental initiatives will continue to be strong elements of the NIH program.

NIH recognizes that there are increasing pressures on the equipment and flexibility of the institutions in which much of the nation's research is carried out. This budget contains an increase of \$5 million to improve instrumentation in extramural laboratories. We will be continuing our review of the research environment this year, in the company of scientists and administrators of their institutions. We hope to discuss the results of this review with Congress in the coming year.

I will close by saying that I am prepared to answer any questions you may have concerning the National Institutes of Health and our 1981 budget request.

TEXT TO ACCOMPANY CHARTS

It is a pleasure for me to be here today to present the fiscal year 1981 budget for the National Institutes of Health.

With your permission, I will submit my opening statement for the record and briefly highlight the more important aspects of the NIH budget.

We have prepared five charts to illustrate the NIH budget picture.

CHARTS A and B

The first two charts graphically display the 1980 and 1981 budgets by SATT categories: Science Base, Applications, Transfer, and Training.

SATT, as explained in previous hearings, is a classification of resources recently adopted by the NIH. We believe it provides a meaningful display of resources by research purpose.

The group of bars to the left is underlined Science Base -- the first of the SATT categories. The Science Base represents fundamental investigation -- the opportunities to extend our base of knowledge from which practical invention must arise.

For 1981, the Science Base is \$2.812 billion. As in past years, research project grants represent the largest single activity supported by NIH.

It is in this area that the Administration has suggested that we maintain a certain number of new and competing grants within the fiscal year. For

this purpose, a sum of \$141 million has been added to the research project grants category over that of 1980. Of the \$141 million, \$112 million is from new money, and \$29 million is from redirection of funds.

This should permit us to maintain approximately 5000 new and competing research project grants and approximately 11,720 noncompeting grants.

The next area within the Science Base includes Categorical Centers at \$305 million and Other Support at \$527 million for 1981. Other Support includes \$5 million in additional funds for the biotechnology program administered by the Division of Research Resources for the subsidy of large instruments that may be used by more than one institution, or by at least more than one department, within a particular region of the country.

In addition, \$1 million has been added for a minority training program, which is a Presidential initiative. This program will create opportunities for minority high school students to participate in research during summer months and, we hope, to be encouraged by that opportunity to choose biomedical research as a potential career.

The last category within the Science Base is Intramural Research, with \$357 million requested for fiscal year 1981. Intramural research is conducted by the NIH itself through its several Institutes. This is an extraordinarily strong program, which remains vigorous and is a benchmark for excellence throughout the scientific community in the United States. For fiscal year 1981, \$5 million and 55 positions will

be added to this category to assist the National Institute of Environmental Health Sciences in the opening of its new facility in North Carolina.

I should also mention that a total of \$8.5 million has been added to the Buildings and Facilities account for the purpose of continuing in FY 81 the essential modernization of the Clinical Center which I discussed with the Committee on January 31, and to begin remodeling five laboratory buildings that are antiquated and far behind safety codes.

The next SATT category shown on the charts is Applications, which represents a set of activities that begin to move knowledge into very practical inventions for application to health maintenance, prevention, and cure of disease. This includes clinical trials. In the Applications category, we are requesting a total increase of \$7 million over the 1980 budget. Certain amounts will increase the capacity of the National Toxicology Program (NTP)—a program developed last year to bring together all the activities of the Department and related departments in the Government for testing the toxicity to man in chemicals in the environment.

The next bar, Transfer, at \$173 million in 1981, represents activities designed to help move innovations into the practice of medicine, and it includes much of the activities of the National Library of Medicine.

Training is the last of the major aggregates of the NIH activities.

Through this program—at \$174 million in fiscal 1981—we provide for the support of some of the people who are essential for renewal of the biomedical research system.

CHART C

I should like to return briefly to an area I mentioned earlier— research project grants. Chart C displays funding for all research project grants for fiscal years 1977 through 1981.

I would call your attention to the shaded area, particularly the comparison between 1980 and 1981. In 1980, we expect to be able to award about 4,750 new and competing grants. In 1981, we hope to be able to fund approximately 5,000 new and competing grants.

The total number of research project grants, including noncompeting grants, for 1981 will be approximately 16,700. This reflects our priority to provide stability and predictability in the Institutes' support of investigator-initiated research.

CHART D

Chart D, entitled "Distribution of NIH Funds, FY 1980 and 1981," graphically compares the NIH budget for the 2 years in question. You can readily see that the Science Base continues to be our primary emphasis.

CHART E

The last chart indicates, for the 1969-79 decade, the numbers of NIH grant applications reviewed, the number of study section members, and the number of study sections.

There has been a precipitous growth in the number of grant applications received and reviewed each year, with an extraordinary 18,700 in 1979, compared to 6,200 in 1969.

We perceive several reasons for this increase in grant applications. First, it indicates the health of the system and the number of people capable of competing for research opportunities. Second, it reflects the need of a larger number of people to compete for grant support as opposed to being maintained in other ways or through other institutions. Finally, there has been a modest increase in the number of applications per scientist within the total received by NIH.

SUMMATION

Mr. Chairman. American biomedical research is of such preeminence today that it has a direct bearing on the quality and length of life of all peoples around the world. It is impossible to define the proper limit to Federal support of such activities. We have made a most thoughtful and earnest effort to reach agreement about the highest priorities among these activities that the fiscal year 1981 budget will support.

The NIH budget reflects the priorities of the Administration--priorities that were reached only after careful and extended discussions with NIH, the Department, and the Administration. I believe the NIH budget addresses the best possible use of available resources to enable progress toward our most important objectives:

- To improve the health of the Nation by increasing the understanding of processes underlying human health, disability, and disease;
- To advance knowledge concerning the health effects of interactions between man and his total environment; and
- To develop and improve methods of preventing, detecting and treating disease.

Thus, the total 1981 budget request for NIH is \$3.582 billion and 11,859 positions. This represents an increase of \$139 million and 62 positions over the 1980 level of \$3.443 billion and 11,797 positions.

I commend this budget to you as an accurate portrayal of the top priority

requirement and needs of NIH and urge its adoption

Again, Mr. Chairman, I am grateful for this opportunity to present the fiscal year 1981 budget request for NIH. I will be glad to answer any questions you may have.

INTRODUCTORY REMARKS
for
DR. THOMAS WALDMANN*

by
Donald S. Fredrickson, M.D.

Good Evening. It is my pleasure to introduce tonight's speaker; Tom Waldmann.

After graduating from Chicago University in 1951, Tom went to Harvard Medical School and then interned at Mass General. From there he came right here as a Clinical Associate, and in the subsequent 24 years has become one of the leading clinical investigators in the world. His landmark discovery of active suppression of antibody synthesis by human suppressor T lymphocytes has revolutionized thinking about the pathogenesis of immune deficiency diseases and has opened up a whole new field of research involving the delicate balance of cell interactions in the immune network.

Tom pioneered in the discovery that autoimmune disease may be caused by defects in the normal homeostatic suppressor mechanisms. On the basis of these findings, he developed an entirely new concept of therapeutic approaches to immune diseases--the concept that certain patients who are immunodeficient may be helped by agents that suppress

* Presented on the occasion of the Mider Lecture in the Masur Auditorium, Clinical Center, NIH, on February 27, 1980.

** Director, National Institutes of Health, Bethesda, Maryland.

suppressor T lymphocytes and, conversely, that patients with excessive immune responses, as are found in autoimmune diseases, may benefit from agents that selectively stimulate the suppressor regulatory cells.

But his work with T lymphocytes is only the latest avenue of exploration in a career notable for its path-finding efforts. In the late 1950's and early 60's, Tom was a member of the NIH team that identified the syndrome "Intestinal Lymphangiectasis." A disease characterized by a generalized disorder of lymphatic channels, leading to excessive gastrointestinal protein loss and to hypoproteinemia and edema. His studies on the pathophysiology of this disease led to an increased recognition of the function of recirculating lymphocytes in immunity.

Tom developed methods to stimulate the in vitro synthesis of immunoglobulin by human peripheral blood lymphocytes in culture and to assay very sensitively--by radioimmunoassays--the antibodies produced. By separating and recombining the several classes of lymphocytes and monocytes, he was able to characterize the separate regulatory roles of T cells and B cells.

Tom's research has also led to new diagnostic tools through the development of the double radioimmunoassay for measuring minute concentrations of alpha-fetoprotein, carcinoembryonic antigen, and human chorionic gonadotropin--proteins that are indicators of human cancers.

The wide recognition of Tom's work is clear from his inclusion among the 300 most-often cited authors of the past twenty years in all fields of science, from the many enthusiastic editorials about his work in prestigious journals, such as the New England Journal of Medicine, from his receipt of numerous honors and awards, and from his many invitations to deliver named lectures.

But a summary of Tom's impact on the NIH would not be complete without mention of his prize-winning photographs which have graced our walls on so many occasions.

We can all name scientists who have made outstanding contributions either in basic laboratory research or in basic clinical research. But it's very rare to find someone who has been so brilliantly successful as Tom has been in merging these often seemingly immiscible disciplines.

Tom's quick mind, his ability to assimilate ideas, his capacity to really concentrate--to pay attention--combined with his willingness to give of himself are among the reasons he has been a constant source of ideas and inspiration for scores of students and collaborators. Some people suspect it has something to do with the mysterious little dog-eared green book of notes he carries with him everywhere.

For all of his many remarkable qualities, Tom has been chosen by his intramural peers for the honor of delivering this year's G. Burroughs Mider Lecture entitled "The Control

of the Immune Response: Regulatory Cellular Interactions and the Control of Lymphocyte Differentiation.

Proceedings of the Public Meeting
March 10-11, 1980

To Address a Proposed Federal Radiation Research Agenda

Volume 1
Issue Papers

Interagency Radiation Research Committee

(Successor to the Committee on Federal Research
into the Biological Effects of Ionizing Radiation)

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Welcome and Introductory Remarks

DR. FREDRICKSON: Good morning, ladies and gentlemen. I'd like to welcome you here this morning, on behalf of a group which represents those agencies of the Federal Government that support and conduct radiation research. I refer to the Committee on Federal Research Into the Biological Effects of Ionizing Radiation. The NIH is just a part of this committee and is very glad to join its sister agencies in sponsoring this important meeting.

This morning we are in a building called the Clinical Center. It serves a dual purpose. It has to be a very good hospital and provide service and care for people who are ill. But it also is a place well-equipped to continue the inquiry, the search for truth that is scientific research. This auditorium represents a similar duality. It is a place where there can be declamations or virtuoso performances by soloists, including coloraturas whose themes come from science or other arts. Of late, it has also become a laboratory for the conduct of experiments that seek to establish some reality or common agreement, particularly relating to the social dimensions of discoveries or inventions that arise from science.

This meeting is one of those searches for consensus. Its origin partly lies in an amendment to the Community Mental Health Centers Act, enacted on November 9, 1978. Tacked on to the end of the Act, as important bits of legislation sometimes are, was a tiny section that said that the Secretary of HEW shall establish a comprehensive program of research into the biological effects of low-level ionizing radiation.

And part of those directions that followed it, brief and terse, included the sentence: "The Secretary shall conduct a comprehensive review of Federal programs of research on the biological effects of ionizing radiation." This was the result of congressional hearings that brought into the open many of the tensions that surround the subject of ionizing radiation and make it also a source of great social and political concern. In these hearings, some criticized and questioned the role of government in managing this kind of research. There was an implied challenge to the credibility of Federal scientific programs, a charge that all of us who are scientists, either active in the laboratory or responsible for program, must take very seriously.

One of the acts that followed this order was the creation of the Federal committee whose long name I've just read to you. Its creator then, almost a year ago, was the Secretary of HEW. Under a memorandum from the President, dated February 21, 1980, this Committee was established by the Executive and moved from its astral status as a voluntary group into a more formal structure that is part of the presidential response to the recommendations of an inter-agency task force on the health effects of ionizing radiation.

The Committee that is sponsoring this meeting is chartered to do several things:

One, it is to coordinate the planning, implementation and evaluation of Federal radiation research programs. It is charged to identify research priorities, to ensure that research is conducted and funded by the appropriate agencies under guidelines developed by the Committee, to assure that the research needs of the regulatory agencies are addressed on a timely basis, to review agency research budgets and comment upon them to the OMB, and to develop criteria for Federal radiation research management following a review of the current and past programs by the National Academy of Science. That review is now being conducted by the Academy through a special committee, some of whose members are here today.

The Federal Committee is also to perform many other tasks related to radiation research. One of these tasks was found, not in the statute itself, but in report language that accompanied the passage of the bill. There Mr. Paul Rogers, then the chairman of the Committee that passed this act, charged the Committee to assess, in consultation with the National Academy of Sciences and appropriate Federal agencies, the needs and direction of future Federal research programs, including the requirements for personnel and funding.

Thus from the hearing record that led to passage of this legislation emerges a fundamental responsibility: the responsibility to shape, to examine and reshape, and project for the future a strategy for the research on the health effects of ionizing radiation.

This is a subject, as I've already indicated, of great concern to many people, not only scientists but to everyone, because of the nature of radiation and the necessary balancing of its obvious benefits and its clearcut potential for doing harm.

Among the issues about which consensus is being sought in this last quarter century, then, are some related to public participation in scientific affairs. Today we hope to exercise, in an appropriate way, that opportunity for people with varied interests and concerns about this subject to listen, to have an opportunity for comment, and to play a role in the development of an agenda for the future of radiation research.

During these last two weeks, we have witnessed a great concern about what the Federal budget for science shall be -- indeed the Federal budget for all kinds of activities -- in the face of the need to curtail inflation. This concern makes this meeting especially important, for it's quite obvious that we'll never have enough funds from Federal or other sources to answer all the questions that are outstanding in our minds.

The need to define priorities and to select those that are most urgent and which can most likely be solved by the application of science is part of our task today and should form a central part of any Federal agenda. The outcome of this meeting will be used to develop this agenda. The strategy that emerges to complete the agenda will be the subject of comment and perhaps change by the same Academy committee that is now reviewing all of the Federal programs for the research into ionizing radiation effects.

The Co-Chairman, along with me, of the Strategy Subcommittee is Mr. Frank Arsenault of the Nuclear Regulatory Commission. I should like to thank him and his committee for the tremendous amount of work performed in preparing this meeting today. Two members of that committee, Dr. Oddvar Nygaard, an expert currently with the Cancer Institute, and Dr. Charles Lowe, a long-time colleague of mine who has been extraordinarily helpful in lending himself to the many staffing and mundane requirements of observing the conduct of both the Academy study and the preparation of the strategy, deserve the thanks of all of us for the effort that has gone into preparing this particular exercise.

We're very grateful, too, for the service of the two persons who will be co-chairmen of this meeting today. Professor Walter Rosenblith arrived at a late moment to rescue us, as your programs will indicate, when Dr. Ivan Bennett could not be present. He is the Provost of MIT, and old hand at matters of radiation and hearings and looking for strategies, and we could not have a better replacement than he.

Serving with him is Peter Barton Hutt of Covington & Burling, whose experience has given him deep knowledge of science as affecting the Federal regulatory process; he is also a veteran of exercises of this kind.

I know that they will bring us through the day and they will extract the most from all of us in attempting to look at a proposed Federal radiation research agenda in the manner that it has been prepared.

So let me now turn the meeting over to the first of our co-chairmen, Dr. Walter Rosenblith. And again, I wish you all welcome and hope that this will be a very good meeting on an extremely important topic.

DR. ROSENBLITH: Thank you very much, Don. Peter Hutt and myself are going to try to be non-invasive and non-repressive Chairmen. The job of the chairman has been defined in a variety of ways. One of them is: to protect the time of the last speaker. We intend to do just that.

Next you will hear from Dr. Upton, who will talk about the background and significance of current ionizing radiation research.

DEDICATION REMARKS*

by

Donald S. Fredrickson, M.D.**

For the mandarins in Washington, March may be the cruelest month. It is appropriations time and carrying thick notebooks we must scurry to the Hill to defend our budgets. From MX-missiles to Medicare, all persons and all "other objects" are atomized to dollars and cents, subtotaled and totaled, and laid out in rows. The fiscal years are stacked sequentially, so that each can be measured on its predecessor. The score of the newest year, the one striving for matriculation, is tallied in the margins. Pluses mark the increases and minuses signify the declines in the line items. These may tell a more faithful story than the Bottom Line. The science budgets, of course, adhere to the common form. There is no place for special marks to indicate the probabilities of a prize or the standard error in predicting discovery. Hypotheses about cell biology or joint pains are lumpy subjects to press into perfect accounts.

The hearings on the fiscal 1981 appropriations for the National Institutes of Health began according to form. On

* Presented at Ceremonies at Yale University School of Medicine on the occasion of the dedication of new Cancer Building in New Haven, Connecticut on March 25, 1980.

** Director, National Institutes of Health, Bethesda, Maryland.

the Senate side of the Capitol, in the elegant quarters of the Senate Appropriations Committee, the numerous Directors of NIH: its three Bureaus, nine Institutes, and one Division which get separate annual appropriations gathered for two days with members of the Subcommittee on Labor, Health, Education, & Welfare, powerful citizens whose places at the baize-covered conference table are each engraved on brass plates at the rim.

Two weeks after the Senate hearings ended, and a few days before the hearings of the House of Representatives began, the first of the "occasional pieces" appeared in the Sunday Washington Post. A reporter had chosen the NIH budget as a vehicle to lead readers through the subtleties of the complex appropriations process.

On February 26, the second round of the proceedings began in Room 2356 of the Rayburn Building, the hearing room of the House Subcommittee on Appropriations for Labor and Health. On eight separate days thereafter, we answered questions from the Chairman, and from the six other Democratic and three Republican members of the Subcommittee, variously in attendance. Periodically, the Post provided further program notes on the participants and proceedings.

At the conclusion, the Chairman observed in his customary and courtly fashion that "We've made a mighty fine record, Doctor. This has been a good hearing."

Yes, as hearings go, we had done well; but things were highly abnormal. The Chairman's last question--to be answered for the record--was: "How would you reduce your budget by \$300 million--where would you take your cuts?" Moreover, a weekend before, several of us had answered an unprecedented early morning summons from the Administration. We were asked to describe, as an exercise in belated balancing of the budget to counter inflation, how we would distribute an even greater reduction in the budget, one spread over the present fiscal year ('80) and the next. During the House hearings we received from some Members requests to display the effects of other experimental formulas for austerity. Then, the Congress suddenly informed itself that it had exceeded its own budget ceilings. Lengthy caucuses and consultations ensued, within and across Party lines, and in the presence of, and the absence of, the Executive Branch. The President announced he had decided upon drastic reductions in the outlays provided by his budget for fiscal '81.

The details proposed by all participants are awaited. And it will be late Spring before recissions and reductions intended to induce deflation and recession are decided upon. It will then take some time longer to learn how well balancing of the Federal budget will ease the economic miseries which afflict us all. It is obvious that science, not being immune to fiscal ills, will not be spared the cure. We have heard predictions that reductions in federal

spending for biomedical research may be more severe than at any time in the history of the National Institutes of Health.

The plans for possible serious shutting-down of parts of the plant--a new experience for biomedical research in America--are the subject of this essay.

The planned responses to any order to throttle down have mixed origins. Many are to be found in recapitulating the autogeny of NIH itself. The agency began before the turn of the century as a very modest Public Health laboratory. It eventually became the National Institute of Health, companion to a recently created National Cancer Institute in Bethesda, Maryland. The metamorphosis to something more than a place for intramural research conveniently occurred in time to benefit from a surge of enthusiasm for continuation in peace time of federal support of scientific research during World War II. By 1950 the National Institutes of Health had become plural, and were on their way to becoming the most powerful supporters and conductors of research in medicine and the life sciences that the World has seen--or may ever see again, depending on the fortunes of the American economy in the years before us.

The mode of change in the annual Federal outlays provided for biomedical and behavioral research in the NIH budget has, in the last decade, tended toward a

stereotype: measured indifference of the Executive calculated to balance persistent generosity of the Legislature. The average Congressional increase in the appropriation over the Presidential request has been 10 percent in the past 10 years. The President's original budget for 1981 had contained the largest increase proposed by the Administration in 8 years.

Although its earlier dramatic rate of growth had declined by 1962, appropriations of some of the several Institutes of NIH have continued to expand selectively. The 1980 appropriation for all NIH was \$3.4 billion. From the signs we've alluded to above, it is conceivable that the fiscal '79 appropriation may have set a high water mark in purchasing power. In constant (1969) dollars, the appropriation level in fiscal 1979 was \$1.6 billion dollars compared to 1.1 billion in 1969. The 1980 appropriation and the President's 1981 budget will permit less support of research than in 1979.

Certainly America has been bullish about health science in the last quarter-century. Its example has inspired other affluent nations to behave similarly, if on a lesser scale. The resulting expansion of knowledge about living things, including man, has been truly spectacular by nearly everyone's reckoning. There have been associated improvements in both the quality and length of human life that must be at least partially credited to these intellectual achievements. Few dare to put bounds on the

potential future growth of knowledge or the conquest of diseases through continued scientific research. The limiting rate will be set by the operating capacity of the total system, i.e., the numbers of scientists and laboratories actively engaged.

No single description can do justice to the complexities of the mechanism that runs predominantly on NIH funds. The dimensions and shape are inexact and always changing. People are the essential instruments of production here and about two-thirds of all the resources goes to buy their ideas, disciplined attention, and services. The many persons and institutions involved also contribute non-Federal resources to the enterprise. The turnover of participants is very high. Many must also engage in teaching or clinical care, duties that both help to maintain, and yet may diminish, their scientific productivity.

The distribution of NIH support can be plotted on numerous axes. In one projection it seems to be spread over a vast domain divided into categorical regions (related to organ systems and other diseases) and non-clinical scientific disciplines which provide the tools for reducing problems of biology and behavior to molecular, more manageable terms.

The cycle of activities can also be projected in other dimensions, as running serially from a less differentiated

"science base," through stages by which discoveries proceed toward development to practical applications, the transfer of the resulting inventions into practice, the sorting through the doctor's bag to learn how tools can be improved, and more recently, to help decide which should be discarded. It is axiomatic that NIH resources also must support the training of new scientists, essential replacements for the professionals now in the system.

To state that NIH has to assure the vitality of the search down through succeeding generations of scientists puts the custodial role too simply. Each field of science also requires an enormous institutional memory that can't be maintained by singing ballads to the young. The mega-bits of information are a mountainous accumulation. They must be kept in orderly heaps for the endless sifting and refinement into knowledge. Nowadays, the treasure is hoarded on magnetic tapes and microfilms, for the paper on which it is displayed has a shorter life than man. The open lines from the past into the future include more than Medline and Index Medicus. Biomedicine is also curator for living bits of ancestral memory. There are special strains of protists, plants, or animals, or cell lines from them, to be passed along. Many of them are mutations that are priceless, irreplaceable experiments of nature. The world's scientific laboratories hold in storage numberless other witnesses to the infinite forms taken by life and their biological products: fluids, molecules, polymers, the viruses, the clones, and the recombinants.

Austerity planning, then, means paying close attention to the whole political economy of a trust maintained in perpetuity for humanity. All the elements--the people, places, and things--contributing to a complex mission of compassionate curiosity have to be given priority ratings. Someone must choose the instruments to be turned off and the memory to be retained.

Recissions will raise new challenges to the educational institutions, down to their very definitions. For example, we have come to think of "teaching hospitals" as generically different from the ordinary kind. Now we hear much talk of "research universities." Can any hospital or university justify perpetuation in the complete absence of teaching and research? What kinds of students emerge from a place where scientific inquiry does not function?

Maintaining the critical role that NIH has come to occupy in America's medical centers is the ultimate challenge in guiding selective reduction in resources. We are many years now into the Post-Flexnerian era. Few of us were alive when the places where the healing arts were taught had no laboratories beyond the abattoir, no libraries other than a shelf of ancient texts and proprietary pamphlets, and no bridges to connect the questions raised by the sick to the answers lying in research. Over these bridges, the health sciences have led the healing arts out of a dark empiricism.

The health of individuals or populations is dependent in many ways, and at crucial times, upon the presence of flourishing scientific endeavor. Where there is proper experimentation there is also candor, skepticism and a drive for excellence. Health care in the neighborhood of research benefits from availability of the most useful and safest specialized procedures, and the knowledge base for wise decisions. From the outset, NIH has based its stewardship of so much of the national capacity for health research on the principle that scientific excellence, as determined by peer review, be the principal arbiter of distribution. No matter what reductions might someday be necessary, we shall want to retain that principle. Distributions by geographical or political formulas are an arch-enemy of quality, yet we shall have to attend to some imperatives while judging excellence. We cannot permit any major area to be impoverished of that expertise in health care that only research can assure.

Special efforts must be made to maintain scientific inquiry where the healing arts are taught. The patient whose healer is a stranger to scientific thought will pay dearly for his doctor's imminent obsolescence.

There is another imperative to keep at the task of correcting inequitable distribution of expertise and opportunity for expression in scientific work among members of some races and cultures in our American population. Some of the schools where high concentrations of minorities

become health practitioners often need special attention in the struggle for excellence that we all have to sustain. These needs would become quite serious in the event of severe fiscal retrenchment.

In its inner ethic, science is forbidden to be sentimental. Where its practice is sustained by contributions from the people, however, science can also not afford to ignore public needs. If there be a right to health, there is also a right to health science. If we must trim the lamp, we have to see that both the light and the warmth are still distributed as widely as possible.

This President is co-author of my text today, and he must provide the next installment. I'm told it will be out this week in the form of an announcement about his proposed changes in the budget. The climax to the piece will be provided by Congress and the President together. We shall provide the denouement.

I've had some preliminary news that NIH may be spared the most pessimistic prospects. The President has indicated that he is sensitive to the need for support of science in many sectors. In the health sciences he has already made decisions in the original '81 budget favoring full support of basic science.

It seems likely that we shall see emphasis on the traditional project grants of NIH's Classic period. Some of the instruments, like the complex centers of the kind we

dedicate today, which were an outgrowth of a later, more Baroque period, will be less emphasized.

The lamp will continue to burn brightly, however.

Yale, a place of excellence, will have both Lux and Veritas.

ON TRIMMING THE LAMP*

by

Donald S. Fredrickson, M.D.**

I.

For the mandarins in Washington, March may be the cruelest month. It is appropriations time and we must scurry to the Hill to defend our budgets. We bear thick notebooks into which all the persons and "other objects" in our charge are atomized to dollars, subtotaled and totaled, and laid out in rows. The fiscal years are stacked sequentially, so that each can be measured on its predecessor. The score of the newest year, the one striving for matriculation, is tallied in the margin. Pluses mark the increases and minuses signify the decreases in the line items, each telling a more pointed story than the Bottom Line. The science budgets, of course, adhere to the common form. There is no place for special marks to indicate the probabilities of a prize or the standard error in predicting discovery. Hypotheses about cell biology or joint pains are lumpy subjects to press into such accounts.

* Presented at Duke University School of Medicine on the occasion of the Stead Lecture in Durham, North Carolina, on April 3, 1980.

** Director, National Institutes of Health, Bethesda, Maryland.

The hearings on the fiscal 1981 appropriations for the National Institutes of Health began according to form. On the Senate side of the Capitol, in the elegant quarters of the Senate Appropriations Committee, the numerous Directors of NIH--its three Bureaus, nine Institutes, and three other units that get separate annual appropriations--gathered for two days with members of the Subcommittee on Labor, Health, Education, and Welfare, powerful citizens whose places at the baize-covered conference table are each engraved on brass plates at the rim.

Two weeks after the Senate hearings ended, and a few days before the hearings of the House of Representatives began, the first of the "occasional pieces" appeared in the Sunday Washington Post. A reporter had chosen the NIH budget as a vehicle to lead readers through the subtleties of the complex appropriations process.

On February 26 the second round of the proceedings began in Room 2356 of the Rayburn Building, the hearing room of the House Subcommittee on Appropriations for Labor and Health. On eight separate days thereafter, we answered questions from the Chairman, and from the six other Democratic and three Republican members of the Subcommittee variously in attendance. Periodically the Post provided further program notes on the participants and proceedings.

At the conclusion, the Chairman observed in his courtly fashion, "We've made a mighty fine record, Doctor. This has been a good hearing."

Yes, as hearings go, we had done well; but things were highly abnormal. The Chairman's last question, to be answered for the record, was "How would you reduce your budget by \$300 million? Where would you take your cuts?" Moreover, a weekend before, several of us had answered an unprecedented early-morning summons from the Administration. We had been asked to describe, as an exercise in belated balancing of the budget to counter inflation, how we would distribute an even greater reduction, one spread over the present fiscal year (1980) and the next. During the House hearings, we received from some members requests to display the effects of other experimental formulas for austerity. Then the Congress suddenly informed itself that it had exceeded its own budget ceilings. Lengthy caucuses and consultations ensued, within and across party lines and in the presence, and the absence, of the Executive Branch. The President announced his decision to reduce drastically the outlays provided by his budget for fiscal '81.

The details proposed by all participants are awaited. And it will be late spring before rescissions and reductions intended to induce deflation are decided upon. It will then take some time longer to learn how well the balancing of the Federal budget will ease the economic miseries that afflict us all. It is obvious that science, far from immune to fiscal ills, will not be spared the cure. We have heard predictions that reductions in Federal spending for biomedical research could be more severe than at any time in the history of the National Institutes of Health.

What are the plans for a possible serious shutting-down of parts of the plant--a new experience for biomedical research in America?

The responses to any order to throttle down will have mixed origins. A number may be found in the history of NIH itself. The agency began before the turn of the century (1887) as a very modest public health laboratory. It eventually became the National Institute of Health (1930) and was relocated in 1938 in Bethesda, Maryland.

The metamorphosis to something more than an intramural laboratory benefited from the enthusiasm for peacetime continuation of Federal support of health research launched during World War II. By 1950 NIH had become plural--the National Institutes of Health--and the aggregate was on its way to becoming the staunchest supporter and conductor of research in medicine and the life sciences that the World has seen--or may ever see again, depending on the fortunes of the American economy in the years ahead.

Although the early dramatic rate of growth in NIH had declined by 1962, appropriations of some Institutes have continued to expand selectively. The fiscal '79 appropriation for all NIH was \$3.2 billion. From the signs alluded to above, it is conceivable that this appropriation may have set the high water mark in purchasing power. In constant (1969) dollars, it was equivalent to \$1.6 billion, compared with \$1.1 billion in '69. The 1980 appropriation and the President's '81 budget will permit less support of research than in 1979.

Certainly America has been bullish about health science in the last quarter-century. Its example has inspired other affluent nations to behave similarly, if on a lesser scale. The resulting expansion of knowledge about living things, including man, has been truly spectacular by nearly everyone's reckoning. The associated improvements in both length and quality of human life must be at least partially credited to these intellectual achievements. Few would put bounds on the potential future growth of knowledge or the conquest of diseases through continued scientific research. The limiting rate will be set by the operating capacity of the total system--i.e., the numbers of scientists and laboratories actively engaged.

No single description can do justice to the complexities of the national mechanism that runs predominantly on NIH funds. The dimensions and shape are inexact and always changing. People are the indispensable instruments of production in research, and about two-thirds of all the resources go to buy their ideas, disciplined effort, and services. The turnover of participants is very high. The many persons and institutions involved also contribute non-Federal resources to the enterprise.

The distribution of NIH support can be plotted on numerous axes. In one projection it seems to be spread over a vast domain divided into categorical regions (related to organ systems and other diseases) and nonclinical disciplines that provide tools to help reduce problems of biology and behavior to molecular, more manageable terms.

The cycle of activities can also be projected in other dimensions, as running serially from a less differentiated "science base" through stages by which discoveries proceed to practical applications. This involves transfer of the resulting inventions into practice, as well as a sorting through the doctor's bag to learn how tools can be improved and, more recently, to help decide which should be discarded.

It is axiomatic that NIH resources also support the training of scientists. Some of these go to the continuous reeducation that is an essential part of being a scientist. Some of the resources must go to train new scientists, essential replacements for those now in the system.

All of us know that the task is not only to invite curiosity and to stimulate the development of disciplined deduction. It is necessary to give assurance to the aspirants that research is a durable occupation, worthy of the investment of a career, indeed a life.

To state that NIH has to assure the vitality of the search down through succeeding generations of scientists puts the custodial role too simply. Each field of science also requires an enormous institutional memory that cannot be maintained by singing ballads to the young. The mega-bits of information are a mountainous accumulation. They must be kept in orderly heaps for the endless sifting and refinement into knowledge. Nowadays the treasure is hoarded on magnetic tapes and microfilms, much more compressed and lasting than paper.

But the open lines from the past into the future include more than Medline and Index Medicus. Biomedicine is also curator for living bits of ancestral memory. There are special strains from among all the protists, plant or animal, to be passed along. There are discrete cells from single tissues, replicating long after the donor is dead. Many are mutants--priceless, irreplaceable experiments of nature. The world's scientific laboratories hold in storage numberless fluids, molecules, polymers, viruses, clones--and recombinants: witnesses to the infinite forms taken by life and their biological products.

Austerity planning, then, means paying close attention to the whole political economy of a trust maintained in perpetuity for humanity. All the elements--the people, places, and things--contributing to a complex mission of compassionate curiosity must be given priority ratings. Someone must choose where the power will be turned off, what is to be the survival order of the mechanisms for research, which memory is to be retained.

II

At NIH we have been anticipating austerity--preparing for it, in fact, back in times when gloom was suppressed because it might become a self-fulfilling prophecy.

The mode of change in the annual Federal outlays that are provided for biomedical and behavioral research in the NIH budget has an oracular pattern. Not the general form, which has pretty consistently tended toward a stereotype: measured frugality of the Executive calculated to balance the generosity of the Legislature. The average Congressional increase in the appropriation over the Presidential request has been 10 percent in the past 10 years. Such oscillations, however, were eventually to be contained in budget ceilings imposed by the Congress on itself. Horizons were converging. Over the years 1975-77, NIH superimposed a new matrix for analysis upon its resource allocations, intensified the integration of forward planning, and quietly added mock drills in reduction.

In 1978 the Congress received a no-increase budget request from the Administration and, in defiance of its experimental, nonbinding budget ceiling, pointedly over-corrected for inflation in the fiscal '79 appropriation. The gap between the Branches was widening. The Secretary of HEW, aware that a crucial corner of his vast budget contained half of the Nation's support for biomedical science, ordered a Department-wide, long-range plan for

health research. Nine-tenths of the Department's \$4 billion for this purpose being the responsibility of NIH, this agency led the effort, but the planning involved all HEW health agencies. In October 1978 hundreds of citizens were invited to Bethesda for a two-day conference. Although lampooned as "peculiarly American," this festival yielded a harvest of principles to guide the Government in using public funds for the health sciences.

The principles had not yet been distilled and distributed when the Congress, this time with pain, increased by 8 percent the NIH budget for fiscal '80. The Administration had proposed a level budget in the face of 9 percent inflation.

During 1979 several intensive negotiations, involving pains and strains of their own, proceeded apace. The NIH Institutes, seeking formulas that both Executive and Legislative Branches might jointly embrace for inducing stability in research funding, finally agreed upon a plan. As a first priority in developing the fiscal '81 budget, NIH would request sufficient funds to put a floor under the power to fund research project grants, and would gain some commitment to this objective from both Executive and Legislative patrons for a period of at least five years.

In a second round of negotiations at the Department, the HEW research agencies sought new ecumenical union around a few interagency initiatives designed to convert the

research funding principles into practice. The Alcohol, Drug Abuse, and Mental Health Administration joined NIH in seeking predictable purchasing power for research project grants.

The "stabilization" initiative became the first of several to survive the second phase of planning. It had two important features for NIH. One, it gave a strong priority to research project grants in reshaping the budget to fit any particular ceiling. Two, it converted this priority into an easily understood and remembered target--a minimum number of new (or competing renewal) grants to be funded each year. The annual goal selected by NIH was 5,000.

The "5,000 grants" survived the hot summer in Washington--even the interruption of the budget development by a change of Secretaries. Lost in the budget's preliminary tour through the astringent vapors of the OMB, the 5,000 were dramatically restored in appeals by the Department. The President's budget unveiled in January 1980 proposed a 4.4 percent rise, most of it earmarked to permit the funding of the new grants. It was the largest increase in a President's budget over the previous NIH appropriation in the last eight years.

In the 60 days between the presentation of that budget and the emergence of its replacement shrunken to effect economies, the 5,000 grants disappeared from the screen on several occasions. The Washington newsletters referred to

expected cuts of some \$350 million in the NIH budget. Cuts of such magnitude would spell a capacity for funding about 3,000 new grants in fiscal '81--half the number awarded in '79. The large community of scientists supported by NIH grants coming up for renewal in '81--and those for new projects seeking initiation--would receive a chilling reception. There were many alarms and excursions behind the scenes.

III

On March 31 the President released his revised budget for fiscal '81. Of the \$550 million stripped from the Public Health Service budget, NIH lost \$90 million. The salvage carried a stipulation: "fund the 5,000 grants."

This landmark restoration, one yet to be placed in perspective by further Congressional actions this year, merits broader explication. As now laid out annually for the Appropriations Committees, the NIH budget contains a half-dozen lines that refer to grants. Since 1969 the largest share has appeared under the label "Research Project Grants." Thus, the "5,000 grants" in the story of the NIH budget for fiscal '81 refers to the investigator-initiated research project grants--R01s, or traditional grants, and P01s, or program project grants, in the codes now employed by NIH.

The "Research Centers" and other lines in which grants may join with contracts or cooperative agreements represent mechanisms of support for extramural research which became important after the first decade of NIH's history.

The extramural dimension of NIH actually began with the creation of the National Cancer Institute in 1937. NCI quickly made some of its funds available to non-Federal scientists in the form of "grants-in-aid." But what I will call the Classical decade of NIH began in 1944, when the

[Figure 1 about here]

statutory genie that has since provided the basic authorities for NIH research and training was created with the enactment of Section 301 (Title III) of the Public Health Service Act. (Figure 1.) The Division of Research Grants was established in 1946 to process applications for grants and to oversee development of a two-tiered system for their review by scientific peers. (Figure 2.) In 1948 the Cancer Institute was joined by Heart and Dental. Before the end of that same year, 1,000 grants were in force, about one-third of them for cancer research.

[Figure 2 about here.]

By 1950 an apparatus for scientific inquiry was being vigorously pulled together. The scale was to be American; a century and a half of indifference would be made up in optimism and generosity. At this time, an important change occurred in the orientation of NIH which dominates it even today: the shift in organization from scientific discipline to the categorical--that is, by disease or organ system.

For example, the Experimental Biology and Medicine Institute became the National Institute of Arthritis and Metabolic Diseases, a title which has subsequently undergone further adumbration as aficionados of other diseases have found it a focus for their attentions. Besides the Cancer Institute, the National Institute of Arthritis, Metabolism and Digestive Diseases and the National Heart, Lung, and Blood Institute (Heart having annexed the Lung in 1969 and the Blood in 1976) have been two of the greatest supporters

of research project grants. Ranking with these is the Institute for General Medical Sciences. This is a descendant of the Division of Medical Sciences, created in 1958 to offset a categorical emphasis that was beginning to threaten continuation of the basic science disciplines vital to mastery of our ignorance of most diseases and the bases of health.

In the Classical period of NIH history, the traditional project grant (later coded R01) was the quintessential mode of doing business. The grants were small. The average cost of each of the 1,500 NIH grants in force in 1950 was \$8,900, and the maximum overhead collected by the institution was 8 percent of the total costs. The best ideas were given financial support, and the scientist was left alone after passing the review on the merits of the proposal. It was a laissez-faire period, and accounting was mainly by gentlemen's agreement. But it was a Puritan or Fundamentalist period, too, in the sense that "program relevance" was muted if the science was judged to be excellent. Big projects, the hot pursuit of the quick cure got a cold reception from the "peers" who, then as now, sit in judgment.

In 1979 the average R01 was budgeted at \$79,000. Compared to the average R01 of \$8,900 in 1950, the cost of R01s has risen faster than inflation. Research has grown more costly to do.

The "unit of research" that is embodied by the 1980 model R01 now coming off the Council approval lines employs about three people, provides around \$42,000 in salaries and other direct personnel costs, and permits \$14,000 to go for purchase of equipment, supplies, and services. It also will bring to its home institution an average of \$24,000 in indirect costs. The average grant is given for a little over three years. This means the principal investigator must finish his application for renewal near the end of the second year. Today's PI has a half-life of about five years in the system. In Classical times, they lasted three times longer.

The second decade of NIH--a Renaissance period

[Figure 3 about here.]

(1955-1965)--was a time of rapid growth in NIH and of new institutional forms. (Figure 3.) The NIH appropriation more than doubled between 1956 and 1957. A concern for institutions became manifest in the creation of general research support grants (1960). Likewise, an awareness of the need for new laboratories was expressed in matching funds for construction, reaching a peak of \$64 million in 1965. Contracts had been used sparingly before, but during this period targeted support grew rapidly. Contract R&D rose from \$4 million in 1957 to \$46 million in 1965.

The research program project grant (P01) was announced with some fanfare in 1962. The first such grant, however, was doubtless awarded long before that, in recognition of

differences in the way individual scientists prefer to work. Some wish to be alone, some flourish in troupes. Nobel Laureates are found at both ends of the scale.

The program project grant supports a number of professional scientists and their work on a central theme or problem. As in the R01, one investigator is the principal. The P01--the model for the first "centers" and for the latter-day "master grants" being tried by NSF--has always been viewed with ambivalence. There are gifted team leaders whose work is best supported in this way. Moreover, the support of a large laboratory (or small department) can greatly reduce the accounting problems attendant upon fragmentation of support into numerous small grants with narrow categorical objectives.

The negative aspects of the P01 are the possibility of overextending too far the shadow of an excessively entrepreneurial "PI," or a masking of mediocre pieces supported within the whole. The vulnerability to sudden extinction of the many whose support derives from a single grant also makes the P01 a riskier bet in today's highly competitive bidding for support of research ideas.

The budgeted cost of the average P01 was \$583,000 in fiscal '79. One P01 thus bumps more than six R01s below the payline. Thus the balance between R01s and P01s must be watched carefully in maintaining the sizable enterprise represented by project grants. In fiscal '70, about 10,000

research project grants (R01s and P01s) were in force and being replenished at a yearly rate of about 2,600. Ten years later, in the vintage year '79, almost 6,000 competing grants were awarded and the total being supported at year's end was 14,600*. About 14,200 of these were R01s. Three percent of the number were the king-size P01s. The percentage of grants that were R01s (94 percent) was steadfast through the 1970s. The proportion of research project grant funds going to R01s in 1979 (80 percent) was slightly higher than in 1970. The two kinds of grants, R01s and P01s, and have thus been increasing in cost at about the same rate over the last 10 years.

Concern for the stability of the capacity to support sufficient R01 and P01 grants grew during the sixties. It was not so much engendered by the declining rate of growth in NIH after 1961, for modest growth was still steady until about 1969. Rather, it was the erratic, asymmetrical growth, and sometimes the bizarre course of both organization and budget, that characterized the decade from 1965 to '75. There is ample justification for labeling this epoch a Baroque period in NIH history. (Figure 4.)

[Figure 4 about here.]

Here are some of the features of the times. The National Institute of Mental Health marched away to become a

* Excludes supplements.

separate research cum service organization in 1967**. Special interests (members of the protean movement called the Disease-of-the-Month Club) gained satisfaction in the creation of new Institutes (Eye and Aging) or mandated programs (sickle cell disease, Cooley's anemia, sudden infant deaths, diabetes, communicative disorders, etc.). Some of these initiatives sought to earmark a greater share of the funds available for R01 and P01 grants; often they helped increase those funds in a general way. Many of the disease initiatives included the urge to create clusters of categorical (disease-dedicated) research centers. Between 1970 and 1975, research center grant support grew from \$98 to \$244 million.

The Granddaddy of all disease initiatives was the National Cancer Act of 1971. It was accompanied by a four-fold rise in the budget of the National Cancer Institute between 1970-1975. The largest proportion of these funds were not allocated to research project grants. The amounts going to "collaborative research" (largely contract-supported) raised anew the old questions of program balance and whether enough untargeted research was being maintained.

By 1975 the Baroque began to cool. Massive experiments to convert NIH into a supervisor of Regional Medical Programs or of health manpower education (a \$530 million

** The programs that have been transferred out of NIH are not represented in the figures.

expenditure in 1973) had come and gone. The schism of NIH threatened by the Cancer Program had been avoided, but the use of massive contracts was exciting the oversight of Congressional committees. A taste for an abundance of project grants was returning. Training and general research support had become bones of contention between the Administration and the Congress, and support for both was declining.

[Figure 5 about here.]

The Contemporary period, from about 1975 to the present, has been marked by certain strong initiatives of its own. (Figure 5.) Some have been related to readjustment of the boundaries of NIH. A confusion of responsibilities became acute in the mid-70s, having diverse origins in concern over technology and cost containment and in diffuse irritation with science, as with all elite institutions. New approaches were taken in the evaluation of biomedical technology and the assuagement of anxieties arising from some scientific inventions. At the same time it became necessary to take steps to prevent regulatory, service, or excessive advocacy missions from damaging the objective setting and sharpness of the scientific instrument which NIH preeminently maintains in the interest of public health.

The Contemporary period has also seen the first real confrontations of NIH with serious budget constraints. The shrinking of budgets due to inflation, the increasingly tenuous support for training and the research environment, the funding of expensive clinical trials, and the exploi-

tation of enormously expanding opportunities in many fields simultaneously have all seemed to converge at the midpoint in this fourth decade of NIH.

Significant new trends in funding of activities have been established in the last five years. The share of NIH research dollars going to project grants has risen, that going to contract programs is declining. Growth of centers has stopped. A trend toward the more traditional mechanisms of the Classical period is in place. Yet scientific needs and opportunities will never be as simple as they were in that now remote time. Compromises are inevitable. Without question, our ability to hold the course depends upon the skills we employ in meeting the challenge of the "5,000 grants" without sacrificing other necessary ways of conducting health research.

The Funding for Grants

A grant is a firm commitment of support for a period of several years. Each year these commitments are met first; applicants for renewal of their grants join those submitting new proposals in competing for the residual of the total funds allotted for project grants. The number of grants awarded each year thus depends heavily upon the annual appropriation, is not predictable in advance, and is subject to considerable variation. The total of grants in the portfolio of a given Institute also reflects several cumulative years of funding.

Throughout the seventies, the number of "new and competing" awards made each year took a jagged course. The bottom (2,590) was touched in 1973 as President Nixon refused to spend all of that year's appropriation. The Congress rejected this attempted rescission, and the number awarded pitched upward the next two years (4,500 and 4,600), fell badly again in 1976 (3,460), and then rose dramatically in 1978 (5,200) and 1979 (5,900).

Annual variations in appropriations for competing grants are affected not only by general changes in enthusiasm toward support of science, but also by uneven popularity of the attack on certain diseases. The capabilities of the several Institutes for funding grants rise and fall asynchronously year by year. Over the last decade, scientists in the disciplines supported by some Institutes suffered greater perturbation in the marketability of their projects than did those supported by other Institutes. The scientists supported by Allergy and Infectious Diseases, for example, tasted three nonsequential years when less than 30 percent of their "approved" proposals could be supported. This capacity was well below the yearly mean (34 to 56 percent) of the Institutes combined during the '70s.

As earlier described, the decision to seek a general commitment on the part of both the Administration and the Congress to strive for a floor of about 5,000 competing grants to be funded annually (about 16,000 total grants per year) was a bid for long-term stability of the single most

important mechanism for supporting extramural research. Because busy laymen must make the key decisions on such a bid, the objective was cast in a form understandable and easily remembered.

During the expansionist years of the '60s, the revered "Dow-Jones Index" of NIH was the "Percentage Funded," meaning the share of approved research projects that could be paid. The ability to pay all good ideas of the Renaissance period had declined to a lesser but still encouraging 50 percent by 1975. But a yearly rise in good grant applications, occurring at a rate exceeding appropriations, portended a dismal annual decrement in this index. Last year's appropriation was based on a quality score: "Payline," or the lowest Study Section priority score of the grants that an Institute expects to be able to support. Because Study Section scores do provide the single most reliable indicator of the quality of research proposals, their use as a guide to funding capacity is commendable. It is almost unbeatable when combined with the other major virtue of the project grant--the fact that it represents experiments considered meaningful by the scientist, as opposed to those appealing to laymen, or government employees. Scientists tend to pick soluble problems to work on--and want them to be important problems, if only because the recognition for successful solutions will be higher. Generally, the problems most popular with the most gifted scientists will be related to fundamentals that extend and enrich the science base.

Relatively few discoveries are chosen to be carried on to practical application.

The defects of either the expected Payline or the Percent Approved index for appropriations lie in the weaknesses of projection. For a decade the number of proposals to NIH has been rising for reasons that doubtless are not a simple function of the number of career biomedical scientists in the system. The curve is not steady, nor the same for all Institutes. It is asking much of an Institute to project, 18 months in advance, the number of approved applications it will receive, their average cost, and the number to go unfunded into the next year's competition. The optimistic Institute can outbid the more conservative one, and appropriations distributed to even out the purchasing power may yield unpredicted asymmetries two or three years later.

The research project grant is also too narrow a base for determining all the adjustments to be made by appropriation committees acting on a proposed budget. The scientific terrain covered by different Institutes is not the same, nor is the degree to which they rely on project grants for their programs. The priority scores given by Study Sections to different kinds of work supported by different Institutes will also differ--by as much as 20 to 30 points. These factors also operate against adjusting the funds in a given Institute's budget to "pay through 200" as the sole determinant of how the support of research should be allocated.

I would be the first to admit that a resort to the device of "supporting 5,000" also creates major problems of its own. A philosophical one lies in deciding how many grants we should support. A practical one is determining how the permissible number of grants are to be distributed among the eleven Institutes. No one has the wisdom to decide this justly, nor should any one person have the power to set this distribution alone. It should be a collective decision, taking into account the total grants supported by an Institute, the recent Payline and Percentage Funded, and the quality of the future projections.

Important, too, are differences in the stages of developments of the various fields, for the more advanced the state of evolution, the greater the need for developmental research that may be funded by other mechanisms. The alignment between needs and opportunities is never perfect. Usually things are sent farther out of line by rationing purchasing power according to the harshness of constituent demands. One hopes, above all, that a constrained system will be a temporary phenomenon, and that numbers of grants, like paylines and percentages funded, will not endure as the principal tools of the philosopher-administrator.

Maintaining the project grant program in full vigor and meeting the intended goals is going to be a major task for NIH in the next two years. If the cost of individual grants continues to rise, the budgets of those awarded will have to

be cut as lean as possible. Some savings may be required from the budgets of grants in the continuation stage. Any rise in the proportion of the grant funds going to indirect costs will tend to reduce the number of scientists that can be supported. This last is a serious matter, for institutional costs are hostage both to the same inflationary pressures as the scientist's costs and to a narrowing of access to other kinds of support to maintain their operations. The President's budget decision of March 31 is a welcome one for scientists whose research is best supported by the traditional mechanisms. All other programs must be reduced, however, in the interest of sustaining the number of project grants.

The President's revised 1981 Budget restored a major amount of resources that could have been removed and which had to be borne by other portions of the budget. Nevertheless, to maintain the project grant program, almost all other mechanisms of support for research and training have been trimmed and will inevitably share the effects of inflation: both categorical and general support centers, training, intramural research, and the National Library of Medicine resource, research and development contracts, clinical trials and other applications of research.

Inflation and the reductions in Federal spending to combat it will raise new challenges to the educational institutions. For example, we have come to think of "teaching hospitals" as generically different from the ordinary kind. Now we hear talk of "research

universities." Can any hospital or university justify perpetuation in the absence of teaching and research? What kinds of students emerge from a place lacking scientific inquiry?

Maintaining the critical role that NIH has come to occupy in America's medical centers is the ultimate challenge in guiding selective reduction in resources. We are many years now into the post-Flexnerian era. Few of us were alive when the healing arts were taught in places that had no laboratories beyond the abattoir, no libraries but a shelf of old texts and proprietary pamphlets, and no bridges to connect the questions raised by the sick to the answers lying in research. Over these bridges the health sciences have led the healing arts out of a dark empiricism.

The health of individuals or populations is dependent in many ways, and at crucial times, upon the presence of flourishing scientific endeavor. Where there is proper experimentation, there is also candor, skepticism, and a drive for excellence. Health care in the neighborhood of research benefits from availability of the most useful and safe specialized procedures, and the knowledge base for wise decisions.

From the outset NIH has based its stewardship of so much of the national capacity for health research on the principle that the main arbiter of distribution is scientific excellence, as determined by peer review. No matter what reductions might someday be necessary, we shall want to

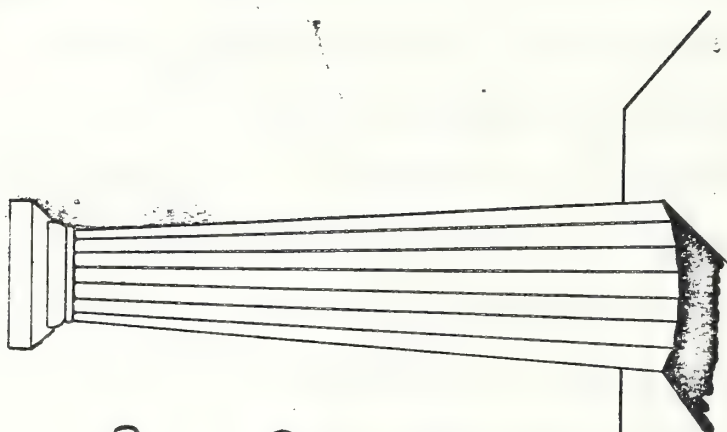
retain that principle. Distributions by geographic or political formulas are an arch-enemy of quality, yet we must attend to some imperatives while judging excellence. For one, we cannot permit any major area to be impoverished of that expertise in health care that only the presence of active research can assure.

Special efforts must also be made to maintain scientific inquiry where the healing arts are taught. The patient whose doctor is a stranger to scientific thought will pay dearly for the imminent obsolescence. This touches upon the imperative to keep at the task of maintaining expertise and opportunity for expression in scientific work among members of the different races and cultures in our American population. Some of the schools where high concentrations of minorities become health practitioners often need special attention in the struggle for excellence. That struggle will increase in the event of severe fiscal retrenchment.

In its inner ethic, science is forbidden to be sentimental. Where its practice, however, is sustained by contributions from the people, science can also not afford to ignore public needs. If we must trim the lamp, we have to see that both the light and the warmth are still distributed as widely as possible. It is also obvious that biomedical research has been spared the worst in the measures that we must all support in the interests of restoring the economy. The search for reality will continue with vigor and success.

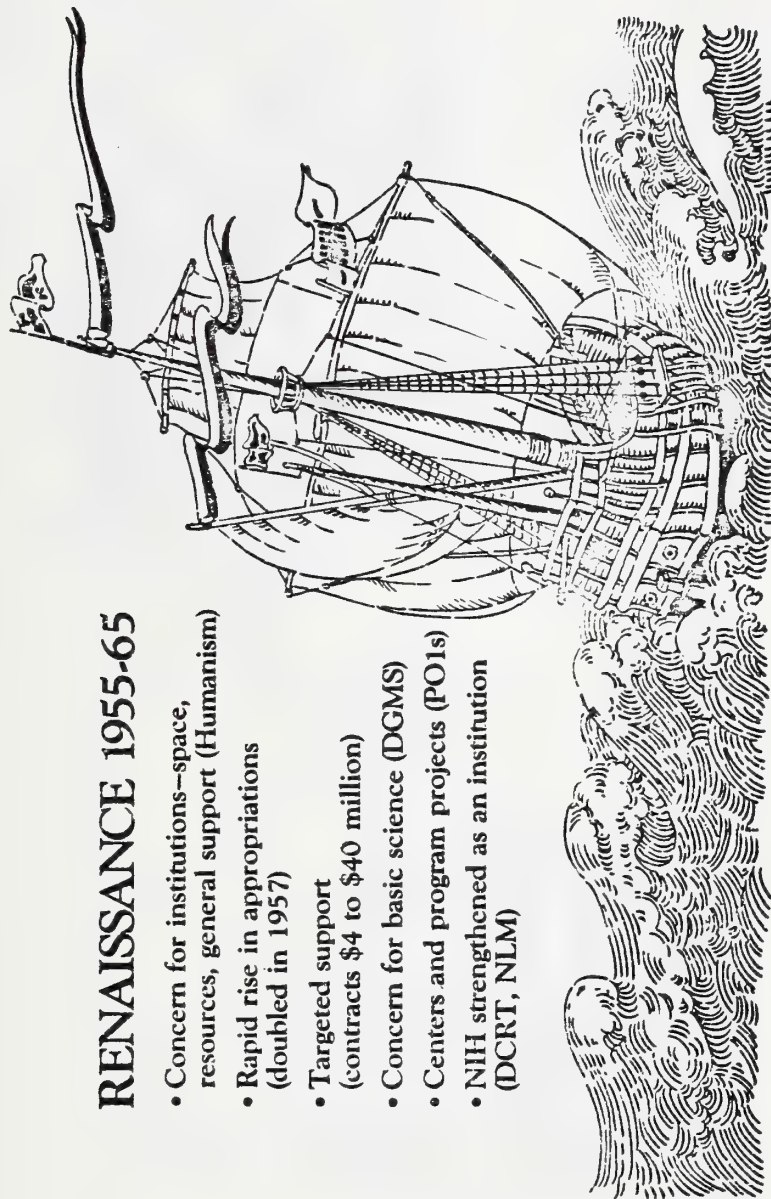
CLASSICAL 1945-55

- Laissez-faire approach (Age of Faith)
- Traditional grants (ROI)
- Central mechanism for grant management (DRG)
- Multidisciplinary fellowships (DRG)
- Orientation shifts from disciplines to diseases



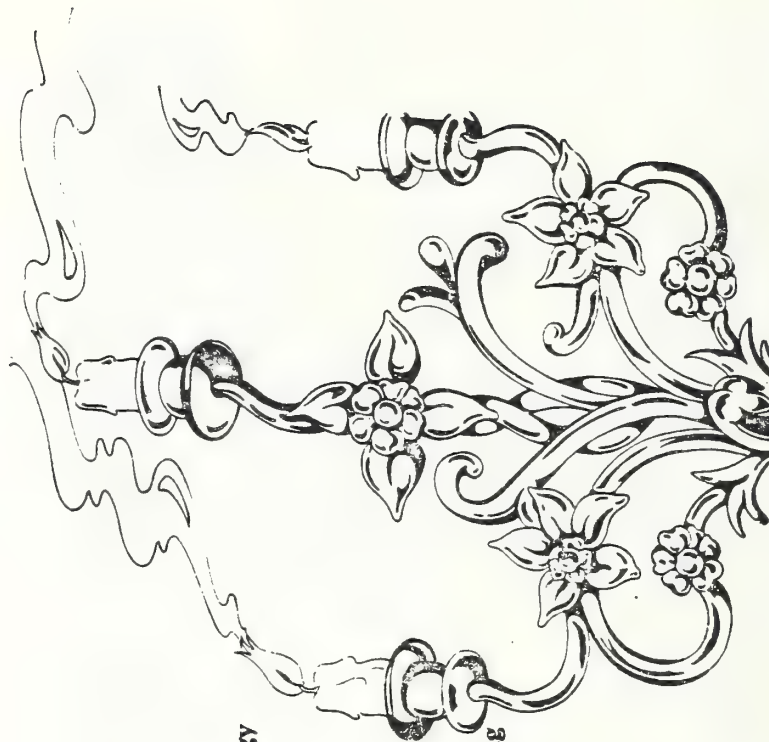
RENAISSANCE 1955-65

- Concern for institutions—space, resources, general support (Humanism)
- Rapid rise in appropriations (doubled in 1957)
- Targeted support (contracts \$4 to \$40 million)
- Concern for basic science (DGMS)
- Centers and program projects (PO1s)
- NIH strengthened as an institution (DCRT, NLM)



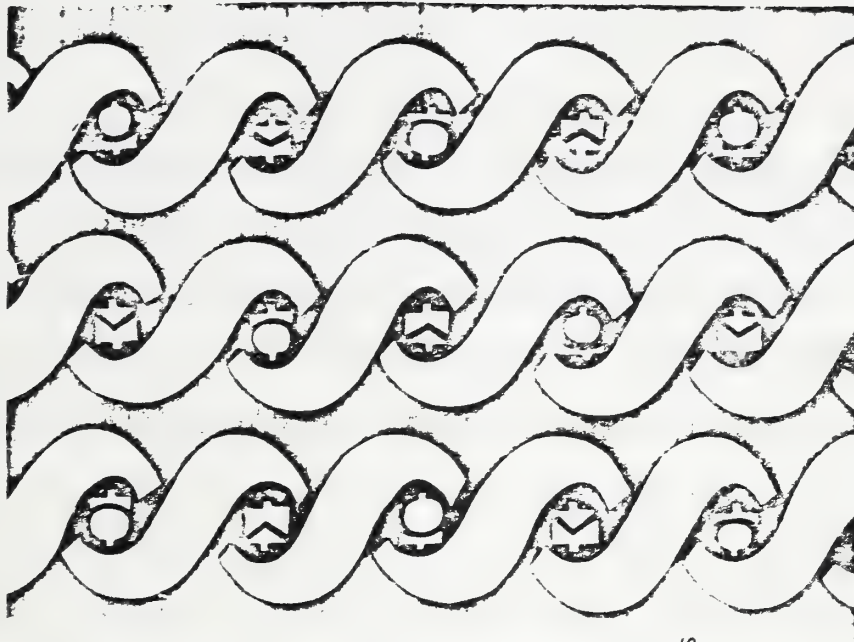
BAROQUE 1965-75

- Slower, bizarre expansion
- NIMH, disease control, and technology transfer (RMP) out
- Responsibility for nation's health manpower (\$520 million in 1973)
- Disease-of-the-month, highlighted by Cancer Act of 1971
- OMB at odds with scientific community on policy—research training and general support



CONTEMPORARY
1975-85

- Level, then shrinking budgets due to inflation
- 1979 peak in constant dollars
- Indirect costs continue to rise
- Period marked by strong initiatives
 - ...technology consensus and transfer
 - ...HEW-wide research planning
 - ...strong program budgeting
 - ...effort to stabilize research grants



5th ANNUAL OBSERVANCE OF SECRETARIES WEEK AT NIH

NIH-wide Program

Wednesday, April 23, 1980
Building 10, Masur Auditorium

REMARKS

DR. FREDRICKSON: Happy Secretaries Day and Week. I am very pleased to be with you today, especially to pay tribute to secretaries and to all those in office support positions. In large measure, the success of NIH depends upon the skills and efficiency of office support staff. All of us are greatly indebted to you for your dedication, hard work, and contributions to our mission. Without you, NIH could not function.

Unfortunately, there seems to be a lot of misunderstanding about the true intention of Secretaries Week. Many think of it as the one time a year that a boss takes the secretary out to lunch! The real intention of Secretaries Week is "professional" recognition, as well as a time of appreciation. The purpose of Secretaries Week is to bring recognition to secretaries for their vital role in business, industry, education, government, and the professions. It also serves to remind secretaries of their responsibilities to their profession. This last phrase, "to remind secretaries of their responsibilities to their profession," has been greatly misunderstood. It does not mean that secretaries need to be reminded to do a good or better job, but instead it means that the secretarial occupation should be thought of as a profession. The Oxford Universal Dictionary defines "profession" as:

The occupation which one professes to be skilled in and to follow; a vocation in which a professed knowledge of some department of learning is used in its application to the affairs of others, or in the practice of an art founded upon it.

Just as physicians have responsibilities to their profession, so do secretaries. The secretary has a responsibility to see that standards of skill and conduct are kept high. The "art" of being a good secretary is a learned skill and demands respect for the knowledge and skills required. Indeed, we all have responsibilities to ourselves, to our spouses, to our parents, to our children, to our employer, etc.

Today, as part of the 5th annual observance of Secretaries Week at NIH, we have what should be a very interesting and stimulating program on sexism. At this time I would like to introduce Mrs. Sally Linn Nichols, CPS (Certified Professional Secretary), who is responsible for arranging today's program . . .

DEDICATORY ADDRESS*

by

Donald S. Fredrickson, M.D.**

On behalf of my fellow workers at the National Institutes of Health, and particularly the National Cancer Institute, I offer my hearty congratulations to Howard University for the accomplishment symbolized by this occasion. I also bring you warmest greetings from one of your many distinguished alumnae, a former dean of Howard University School of Law, who is now my boss. I speak, of course, of Secretary Patricia Roberts Harris.

Dr. Woods, for whose kind introduction I am grateful, also has close ties with the National Institutes of Health. She served on one of our principal advisory committees and continues to be an important counselor to us.

It is indeed a pleasure for me to join with President Cheek, Vice President Alexis, Dean Miller, Director White, Dean Crawford and all of their colleagues in these dedicatory ceremonies.

* Delivered on the occasion of the dedication of the Cancer Center, Howard University, Washington, D.C. on April 24, 1980.

** Director, National Institutes of Health, Bethesda, Maryland.

I want to mention especially a person to whom this occasion must have special meaning -- your alumnus and Chairman of Surgery, Dr. LaSalle Leffall, the immediate past President of the American Cancer Society.

The dedication of a major facility to the search for truth and in the service of humanity is an occasion for much pride and joy. As I was riding my bicycle to work this morning -- I hope the Secretary and the President are listening -- I thought of the importance of this occasion. Riding under the trees, I was also reminded of John Donne's poem about the ashes of the great oak in the chimney, and how they did not reflect the comfort afforded birds and animals by that tree, or the shade it offered to many for generations. So is it true of the image of the handsome building behind us. It is only symbolic and doesn't give the full dimensions of its importance. The occasion is akin to the day the librarian at Yale noticed with chagrin that a large number of the local gentry had stopped on the street to admire the new library. Charging outside to the steps in front of the building, the librarian startled the onlookers with the irritated shout, "What you see is not the Sterling Library. The Sterling Library is inside."

And the Center we dedicate today is not just the result of the professional skill of the architects and the competence of the contractor. It is the ideas, the imagination, the perseverance, and the dedication of the occupants of this Center that will determine its true value to Howard, to the community, and to mankind.

If the Director of your Cancer Center, Dr. Jack White, had not been at Howard, working as hard and ably as he does every day, we would not have been here for a building dedication. Most of you know what he has contributed, but I should tell you that many other people also appreciate his invaluable role in the creation and growth of this Cancer Center.

Obviously, Jack White alone could not have brought this Center and this building into being. He was blessed with unusual cooperation and assistance from Howard University's Trustees and President, from the Medical School administration, and notably from community leaders, all of whom have helped to more than double the financial resources of the Cancer Center within the last two years. His scientist colleagues at the Center and in the Medical School and Hospital have been most supportive. I mention particularly Dr. Carrie Hunter who directs the clinical

programs, C. Godfrey Jacobs, Associate Director for Community Outreach, and also the two new Associate Directors, Dr. Roscoe Moore for Epidemiology and Biostatistics and Dr. Kenneth Olden for Basic Research.

This new building represents the culmination of an eight-year old dream. Your Comprehensive Cancer Center was recognized by the National Cancer Institute in 1974. Along the way the Cancer Institute provided funding of almost \$6 million for the construction, which began in 1977. Until the new building was ready for occupancy late last year, the center had been housed in various and separated sections of the College of Medicine and Hospital. Now Howard joins other university-based cancer centers having an identifiable center building.

This new six-story structure with 35,000 usable square feet of floor space presents you with an enviable opportunity for expansion and closer coordination of cancer research activities. I've been told that it contains more than 40 laboratories and 60 offices, in addition to the radiotherapy, nuclear engineering and bioengineering units with their sophisticated equipment which are housed in the basement. The completion of Howard's construction program, after years of

careful planning, will give to its cancer mission a greater opportunity for the coordinated activities that are so vital to the development of a truly multidisciplinary major center. Cancer centers have become a unique national resource, and have inspired the development of comparable centers by other NIH institutes for other serious health problems, including heart disease, diabetes and arthritis.

Last June, in testimony on "cancer in blacks" before a Congressional Committee, I remarked on the perplexing and terribly important public health issue -- the disparity between black and white populations with respect to cancer incidence and mortality. The rate at which cancer strikes black males is higher than for any other race/sex group. Black females, on the other hand, are shown to have less cancer than whites of either sex. However, cancer death rates are greater for blacks than whites regardless of sex, with excessive rates starting in 1950 for females and 1956 for males.

As I am sure many of you know, a leader in epidemiology comparing cancer rates in black and white populations has been the National Cancer Institute. NCI has also published two Atlases of cancer maps to help stimulate further research.

Currently we are conducting and supporting studies among the black population. NCI is presently collaborating with medical schools and hospitals to study cancer of the esophagus among blacks in the District of Columbia to try to learn why the rates of this form of cancer are higher here than in other urban areas. There are similar studies under way in Los Angeles and in New Orleans.

Howard has always had a very strong commitment to decreasing the high incidence of cancer in Washington's predominantly nonwhite area, and the research possibilities provided by Howard's access to this population are unique. Scientific interest in this perplexing public issue is constantly mounting, and Howard has contributed substantially to this progress.

In 1973 Howard University investigators led by Dr. Marvin Jackson began a program to study prostatic carcinoma among blacks. The initial project was to compare, with more than 200 age-matched pairs of men, the incidence of prostate cancer in Washington, D.C., with that in Nigeria. The study revealed a higher incidence of invasive carcinoma among Washington blacks. The findings point to unknown causal factors more prevalent in the western world than in the African continent. Currently,

Dr. Joseph Kovi is studying 200 cancer patients and 200 age-matched controls to explore some possible etiologic factors in the high-risk American black population, including dietary and lifestyle habits.

What your Cancer Coordinating Council for Metropolitan Washington has already accomplished with support from NCI's cancer control division represents a major step in establishing a baseline for future research in cause and prevention. This Council is part of the outreach program of the comprehensive cancer center of Howard and Georgetown Universities. It has completed a study comparing nonwhite cancer mortality among ten major U.S. metropolitan areas for the period 1969-1971, and a similar study within the city of Washington, 1971-1976.

Howard's extensive cancer control program is targeted primarily at the nonwhite population and especially at nonwhite men because of their high cancer mortality rates in the District of Columbia.

Howard's contribution to understanding and control of cancer, through its emphasis on education and training, is highly significant. Dr. Cheek, in inviting me to dedicate this new building stated in his letter: "Its conception extends back to

the early days of the cancer teaching project grants made by the National Cancer Institute to Howard University." Ever since these grants were made more than 30 years ago, Howard has been productively committed to cancer education. For the past four years it has made good use of NCI's clinical education grants. Substantial benefit has accrued to Howard's cancer education programs from the activities of its comprehensive cancer center. Medical and dental students are getting cancer instruction and basic and clinical research exposure that will spin off into whatever medical communities they serve.

Inflation, and reductions in Federal spending to combat it, recently have caused us to assess the priorities for usage of those national assets for health science of which NIH is the steward. There will arise from inflation, or the efforts to fight it now being led by the President, a need for some sacrifices. There will arise new challenges to educational institutions. For example, we have come to think of "teaching hospitals" as generally different from the ordinary kind. Now we hear much talk of "research universities." Does any hospital or university deserve the name in the absence of teaching and research? What kind of students emerge from a place where scientific inquiry is absent?

Maintaining the critical role that NIH has come to occupy in America's medical centers is the ultimate challenge in guiding selective reduction in resources. We are many years now into the post-Flexnerian era. Few of us were alive when the healing arts were taught in places that had no laboratories beyond the abattoir, no libraries but a shelf of old texts and proprietary pamphlets, and no bridges to connect the questions raised by the sick to the answers lying in research. Over these bridges, the health sciences have led the healing arts out of a dark empiricism.

The health of individuals or populations is dependent in many ways and at crucial times, upon the presence of a flourishing scientific endeavor. Where there is sound experimentation, there is also candor, skepticism and a drive for excellence. Health care in the neighborhood of research benefits from availability of the most useful and safe specialized procedures, and the knowledge base for wise decisions.

Special efforts must also be made to maintain scientific inquiry where the healing arts are taught. The patient whose doctor is a stranger to scientific thought will pay dearly for the inevitable obsolescence. This touches on why we must keep at

the task of maintaining excellence and opportunity for expression in scientific work among members of the different races and cultures in our American population. Some of the schools, like Howard, where high concentrations of minorities become health practitioners have an enormous role to play in bringing up minority people to take their rightful place in the main stream of science.

In its inner ethic, science is forbidden to be sentimental. Where its practice, however, is sustained by contributions from the people, science is committed to serve public needs. If we must trim the lamp, we have to see that both the light and the warmth are still distributed as widely as possible. We must work hard together to see that the light burns ever brightly in this place.

* * * * *

It is with honor and pleasure that I formally present your new Cancer Center to you. I am confident that it will fully realize the promise implicit in Howard's tradition of splendid efforts and outstanding results.

REMARKS BY DIRECTOR, NIH FOR DEDICATION OF BIKEWAYS
DURING MONTGOMERY COUNTY BIKE DAY AT NIH SUNDAY 27 APRIL 1980.
NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

TODAY MARKS MORE THAN THREE YEARS OF COOPERATION BETWEEN NIH AND THE MONTGOMERY COUNTY DEPARTMENT OF TRANSPORTATION IN THE DEVELOPMENT AND PROMOTION OF BICYCLE COMMUTING.

WE'RE DELIGHTED AT NIH TODAY TO SEE THESE COMBINED EFFORTS, ASSISTED BY COUNTY BICYCLISTS, BROUGHT TO FRUITION.

WE'RE ALSO DELIGHTED THAT OUR NIH NEIGHBORS (THE NAVAL MEDICAL CENTER, THE UNIFORMED SERVICES UNIVERSITY OF HEALTH SCIENCES, THE SCOUT REGIONAL HEADQUARTERS, SUBURBAN HOSPITAL AND OTHERS IN THE AREA) WILL BE ABLE TO BENEFIT FROM THE COUNTY'S BICYCLE NETWORK.

AND WHEN THE MEDICAL CENTER METRO STATION IS COMPLETED WE ANTICIPATE A NUMBER OF NON-NIH BICYCLISTS WHO WILL ALSO BENEFIT FROM THE COUNTY'S BIKEWAYS AS WELL AS THOSE BIKEWAYS THROUGH THE NIH CAMPUS.

SINCE THESE BICYCLE EFFORTS BEGAN THREE YEARS AGO, WE HAVE SEEN THE NEED FOR ENERGY CONSERVATION BECOME EVEN MORE CRITICAL. THE COST OF GASOLINE HAS CONTINUED TO ESCALATE, AND AT NIH AND THE NAVY, PARKING FEES HAVE BEEN INITIATED. WE HAVE NOTICED AN INCREASE IN THE NUMBER OF OUR EMPLOYEES WHO HAVE TURNED TO THE BICYCLE "TO BEAT" THE ADDITIONAL EXPENSE OF TRANSPORTATION.

MR. GILCHRIST AND MR. CLARK, I COMMEND YOUR DEPARTMENT OF TRANSPORTATION FOR THE WORK THAT HAS BEEN DONE IN PLANNING, DESIGNING AND CONSTRUCTING THE BIKEWAY COMPLEX THAT WE DEDICATE TODAY. I ALSO COMMEND MEMBERS OF MY OWN STAFF, MR. ROSS HOLLIDAY AND

PAGE 2 OF 2

MR. TOM COOK FOR THEIR EFFORTS IN DEVELOPING THE ON CAMPUS BIKEWAY THAT IS JOINED WITH THE COUNTY'S DURING THIS DEDICATION.

WHEN OUR MAJOR CONSTRUCTION IS COMPLETED WITHIN THE NEXT YEAR, WE WILL COMPLETE THE NIH ON CAMPUS BIKEWAY COMPLEX.

I ALSO PLEDGE NIH'S CONTINUED SUPPORT OF THE COUNTY IN PROVIDING MORE, BETTER AND SAFER BIKEWAYS. BUT THEN I CAN'T THINK OF A MORE APPROPRIATE ORGANIZATION THAN THE NATIONAL INSTITUTES OF HEALTH TO TAKE THE LEAD IN SUPPORTING A FORM OF TRANSPORTATION THAT PROVIDES A MOST DESIRABLE HEALTH BENEFIT.

Sorting Out the Doctor's Bag

Donald S. Fredrickson

From the U. S. Public Health Service, National Institutes of Health, Bethesda, Maryland

It is a pleasure to address this first scientific meeting of the Society for Clinical Trials. I congratulate Dr. Roth and the other members of the Board of Directors on having founded, in so timely a fashion, a new forum for discussion of important problems. I remember our surprise at the popularity of the National Conference on Clinical Trials Methodology [1] held at NIH in 1977, and that, in his closing remarks at that meeting, Dr. Roth emphasized the need for just such a society as this.

The general relationship of clinical trials to the organization of the doctor's bag is obvious, and my title was chosen to allow me to sample a full range of ideas. First, though—as I see so many young faces in the audience—I wonder if everyone knows what a doctor's bag is? In ancient times when doctors went on house calls, they carried black satchels containing most of what was useful: diagnostic instruments, bandages, and nostrums. In many cases, anything that could be done anywhere could be done in the home with the contents of the bag.

Times have changed. The CAT scanner, the Anger camera, or the cardiac catheterization laboratory cannot be crammed into a bag. Nor is there room for all the potent drugs now useful in treatment. The bag has become the medical center, replete with equipment tended by a corps of specialized technicians. There are consultant specialists of every type, shelves of medicinal preparations that dwindle into the distant depths of the pharmacy, and endless ancillary services. The modern doctor—in the urban setting at least—no longer carries his bag. He moves around inside it, and feels insecure when outside its walls. It is no wonder that house calls are becoming a rare recollection of another age.

Another consequence of the burgeoning content of the doctor's bag is that medical costs are rising. They are rising fast enough to have become a major focus of attention in recent years. When it becomes technically possible to do more for the patient, we feel compelled to do more, regardless

Presented at the Combined First Annual Scientific Session of the Society for Clinical Trials and Seventh Annual Symposium for Coordinating Clinical Trials at the Philadelphia Marriott Inn on May 6, 1980.

Dr. Fredrickson is the Director, National Institutes of Health, Bethesda, Maryland. Address reprint requests to Dr. Donald S. Fredrickson, Director, National Institutes of Health, Bethesda, MD 20205.

Received June 19, 1980; revised and accepted July 17, 1980.

of expense. Over the past decade, health industry costs in the U.S. have risen at a higher rate than inflation. A large portion of this must be attributed to the availability of services that could not have been offered ten years ago. If we extrapolate from figures collected over the past few years, it is a fair estimate that this year will see our nation spending over 200 billion dollars on health [2]. Such an expenditure will account for just about 10% of the Gross National Product.

Most of us have begun to ask serious questions about the necessity of all this expenditure. Many of us have been asked to help quantify the benefits. More and more skeptics, once without, and more recently within the community of scientific medicine, are beginning to ask searching questions about health practices and the utilization of medical facilities. Last week's issue of the *New England Journal of Medicine* devoted two special articles [3,4] and an editorial [5] to the question of utilization of medical intensive care units. There was evidence that it might be possible to identify patients who do not require the elaborate, sometimes dehumanizing, and always expensive service that intensive care is set up to provide.

Over the past five years, a series of studies by Wennberg, Gittelsohn, and their colleagues [6] have utilized epidemiologic methods to examine patterns of health care utilization among neighboring communities in Vermont and Maine. They seem to show that the principal determinant of the number of operations is the number of surgeons, and the chief factor governing hospitalization is the number of hospital beds. None of these variables is well correlated with a specific health need. Nor do those populations whose utilization rates are higher have demonstrably better health. There is a dearth of supporting information about "health outcomes"—that dry, impersonal statistic popular with health economists. I am reminded that my one-time colleague at the National Institutes of Health, Dr. Howard Hiatt, has established a center within the Harvard School of Public Health whose whole purpose is explained by its title, Center for the Analysis of Health Practices. These investigators are all declaring the need for objective, scientific analysis of the effects of practices on outcome, and rejecting the simplistic argument that runs, "If it can be done, and if it might do some good, it is imperative to do it."

We are also becoming progressively more aware of the subtle adverse effects of some medical measures. In large part this has resulted from controlled clinical trials that have already been done. There are many who are now members of this Society and of this audience who have contributed to such understanding. There is no escaping now a relentless trend toward objective evaluation of the benefits, costs, and risks of the procedures and medicines that doctors administer or prescribe.

Why do we now have such a body of "accepted medical practice" that seems to lack an objective scientific basis? To some extent, the reasons are historical. The biostatistical analytic procedures that you are all so familiar with are of relatively recent vintage. Many practices that are still in common use were introduced at an earlier time. In the past, the provision of health care in this country has always been highly decentralized. Even though an individual doctor or patient has often sorely wished to know if one possible

course of treatment was better than another, he was in no position to find out. Individual experience, one doctor's recollection of the outcome of similar patients he had treated before, had to be the basis for making many decisions. The sample size was limited to the collection possible in one lifetime and usually fell far short of statistical requirements. The possibilities for bias affecting medical judgments were—and remain—limitless.

There is no need to tell this audience how complex, time-consuming, and expensive a scientifically sound clinical trial can be. The sponsor of such an effort must be both well endowed and strongly motivated. These conditions can be met by industry, and many clinical trials have had industrial sponsors. However, the interest of industry is aroused only when the trial concerns one of its products. If the trial shows the product to be beneficial, subsequent profits from the marketplace are expected to cover the costs of the trial.

I believe that current trends in the organization and financing of health care are such that it will become progressively more feasible to find nonindustrial sponsorship for clinical trials. Doctors are now engaging in solo practice less and less and are associating more and more into group and health maintenance organizations. The rise of third-party payers, both public and private, concentrates financial responsibility, and with it financial capability. The Federal government is assuming increasing responsibility for payment of the nation's health bills, and currently either provides directly, or pays for indirectly, about 25% of the total. Most of this is underwritten by the Medicare and Medicaid programs, which the Congress has authorized under the Social Security law. A smaller portion is in direct provision of health care to designated Federal beneficiaries such as veterans, military personnel and their dependents, merchant sailors, and native Americans who remain on reservations.

The Congress has approached the evaluation of health practices cautiously, and has specified in the Social Security law that it does not intend for the Federal government to regulate medical practice [7]. However, for the last ten years the PHS Act has contained a provision for the use of up to 1% of program funds, as designated by the Secretary, for the evaluation of the effectiveness of its health programs [8].

There is no such general authorization for evaluation in the Social Security Act, but a recent modification, the 1973 amendments that established the End Stage Renal Disease program, does contain instructions for experiments designed to control costs [9]. The End Stage Renal Disease program, as you probably know, is unusual in that all patients with a specific diagnosis become Federal beneficiaries, without reference to any other qualifications. It is a paradigm of what might develop under a totally nationalized medical insurance system, and it has proved costly. In setting up the program, Congress requested three studies, two of which address questions of medical technology, and one of which deals with organizational aspects of the delivery of care. All three are oriented toward increasing efficiency and controlling costs.

The decade of the 1980s, I predict, will bring increasing interest in, and pressure for, the performance of such studies. If they are well-designed,

experiments of this type should amortize their own costs with savings in health costs in subsequent years. Thus with suitable accounting, such trials should show a "profit." The main question to be resolved now is how to establish the accounting system that will make it possible to provide the initial investment needed to initiate a self-amortizing trial. I do not believe that the ordinary research budget of the National Institutes of Health can support many of the clinical trials that should be done in the future. The NIH can best concern itself with clinical trials that will either bring novel medical techniques to practical application for the first time, or will provide new insights into the mechanism or natural history of disease. I see no shortage of important questions that fulfill one or both of those criteria.

I do believe, however, that NIH should be prepared to play a catalytic role in assuring the scientific quality of trials that have a primarily economic motivation. We can do this by mobilizing expertise on not only the purely medical, but also the organizational aspects of clinical trial methodology. I expect that this Society, and its membership, will help supply invaluable resources and collaboration to this function.

Efficiency-oriented trials, if I may use that term to designate those aimed at cutting costs without sacrificing results, will contrast in interesting ways with the outcome-improvement trials with which we are more familiar. One obvious difference will be that in their design, ethical problems will probably outweigh technical ones. We may have to withhold an accepted treatment from a test population to learn whether, in fact, it is needed. The studies published in the *New England Journal of Medicine* mentioned previously lead us to ask whether we should now randomly divert some of our low-risk patients with myocardial infarction from the intensive care units to the regular wards, and then carry out long-range observation of patients treated in the two different ways. Such a trial seems logical, reasonably safe, and may reveal unsuspected benefits. Yet, I am sure you can anticipate the recruiting problems that will be encountered.

In a comparison of treatments, the simpler, cheaper, or more conservative one is naturally to be favored if it does not yield an inferior therapeutic effect. In efficiency-oriented trials, then, the design must seek to minimize what you like to call a "type II" error [10], the running of a trial that is not sensitive to a difference that actually exists between the treatment outcomes. Although one could generally say this of all clinical trials, the results of an efficiency-oriented trial should never be published without complete analysis of the power of the statistical tests that were employed in the interpretations.

It is now a dozen years since I characterized clinical trials as *ordeals* [11]. Essentially all the criticisms I made then are still applicable. In spite of the difficulties that they impose on us, however, the need for clinical trials has only continued to grow. They are scientific exercises that provide society with the opportunity for both a unique degree of participation and of benefit. The lessons learned from both successful and unsuccessful trials in the past must be brought to bear on the design and execution of those that lie before us. I foresee a vital role for this Society, its meetings, and its journal, in ever-improving the outcomes of the quest for this kind of knowledge.

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INTRODUCTORY REMARKS*

by

Donald S. Fredrickson, M.D.**

It is a great pleasure to welcome home our old friend Dr. Baruch Blumberg.

Since Dr. Blumberg's important research accomplishments have spanned such a broad field of medicine, it might be interesting briefly to review this unusual man's unusual career.

After obtaining his degree at Union College in New York in 1945, he entered the Navy and eventually became Commanding Officer of a ship called the USS LCS(L)36! As a logical consequence of his naval career, he then spent a year at Columbia University studying mathematics. This naturally led to his entering medical school at the same institution where he received the M.D. degree in 1951. He followed medical school with a house staff appointment at Bellevue Hospital and further clinical work at Presbyterian Hospital. In 1955 Dr. Blumberg left for Balliol College, Oxford, where, under Professor Sandy Ogden, he obtained a degree in physical chemistry in 1957.

Dr. Bunim, then Clinical Director of NIAMDD, having followed Dr. Blumberg's work that had resulted in several important publications in rheumatology and a thesis on joint fluid viscosity,

*For presentation at the NIH Lecture, May 7, 1980, Masur Auditorium, National Institutes of Health, Bethesda, Maryland.

**Director, National Institutes of Health.

invited Dr. Blumberg to join the Arthritis and Rheumatism Branch in 1957. There Dr. Blumberg, with his customary nose for the different, began studies on the antibodies which developed in patients who had been repeatedly transfused. He came across a variety of unusual and interesting antibodies, including one to a lipoprotein and one to a totally unknown protein. Meanwhile, Dr. Blumberg had also developed an interest in polymorphisms and was busily exploring them in appropriate populations such as Alaskan Indians, Australian aborigines, South Sea Islanders, etc. In this way, he discovered that the curious unknown antigen, responsible for eliciting the antibody response, was prominent in some Australian natives, so he named it Australia Antigen. About this time, 1964, the Institute for Cancer Research in Philadelphia managed to lure Dr. Blumberg away from NIH and there he pursued his studies with the result we all know. Australia antigen was indeed one of the hepatitis B proteins and its use as a marker for the diagnosis of this disease has been both a scientific and clinical landmark. Tonight, Dr. Blumberg will present the most recent chapter in this interesting saga whose beginning we were privileged to witness.

VISITING NURSE ASSOCIATION
80TH ANNIVERSARY LUNCHEON
in Honor of
Mrs. Harold N. Marsh*

by

Donald S. Fredrickson, M.D.**

This morning I was visited by two ghosts. Both of them had made an impression on my life; one quite considerably so.

The first was Adlai Stevenson. He visits me often in the morning when I put on my brown shoes -- the ones with the hole in the sole.

Today was special, however, because I was due in the Russell Building of the Senate to appear before Adlai Stevenson, the IIIrd -- a slightly smudged, but nevertheless faithful, copy of the Governor (the IInd).

He was to be the center and I an actor in a little morality play -- a hearing on the regulation of experiments to put foreign genes in bacteria.

Science is often, now, before the public, trying to explain what it thinks it's about.

(This morning I was making my 70th or 80th appearance before a committee -- I've lost count.) I'm

* Held at the Four Seasons Hotel in Washington, D.C. on May 20, 1980.

** Director, National Institutes of Health, Bethesda, Maryland.

getting to be philosophical about them -- a dangerous state. We also have to be careful about not obviously playing roles. Today I was yielding to temptation, slipping into judgments of what this scene meant in the course of mankind.

I lean to Immanuel Kant in classifying moods about where civilization is going. Disputation of the Faculties, 1798; "Is the human species in continuous progress toward the better?"

A regulatory agency -- "moral terrorism."

A Scientist (I heard myself talking) -- a "endeamonist" -- a philosopher of perfectibility.

The Abderitist -- Senator -- circular -- neither better nor worse -- Ixicon's Wheel.

The scientist-optimists -- can the mood be separated.
Is science inherently good?

Then my mind fractured again -- South Bos

Adlai III

Mrs. Ives

My mother -- The Second Ghost never a political animal

- Nurse

- Framingham Union

- Scrubbing floors as probationer

- Formidable supervisors
- School Nurse -- Ford - Model A
- Her talk of Medicine turned me to law!

Her fatal illness a year ago gave me reason and opportunity
to think and to feel more deeply about

- technology
 - CAT Scan
 - relief of edema
 - the 8 years of added full life
- the essential link, the caring
last days the soothing
 sympathy
 love of near strangers

VNA

You, what you do, your transfer, permits me to
be _____ as a scientist.

INDUSTRIAL APPLICATIONS OF RECOMBINANT DNA
TECHNIQUES

HEARING
BEFORE THE
SUBCOMMITTEE ON
SCIENCE, TECHNOLOGY, AND SPACE
OF THE
COMMITTEE ON COMMERCE,
SCIENCE, AND TRANSPORTATION
UNITED STATES SENATE
NINETY-SIXTH CONGRESS
SECOND SESSION
ON
INDUSTRIAL APPLICATIONS OF RECOMBINANT DNA
TECHNIQUES

MAY 20, 1980

Serial No. 96-105

Printed for the use of the
Committee on Commerce, Science, and Transportation



U.S. GOVERNMENT PRINTING OFFICE
WASHINGTON: 1980

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INDUSTRIAL APPLICATIONS OF RECOMBINANT DNA TECHNIQUES

TUESDAY, MAY 20, 1980

U.S. SENATE,
COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION,
SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND SPACE,
Washington, D.C.

The subcommittee met at 9:30 a.m. in room 224 of the Russell Senate Office Building, Hon. Adlai E. Stevenson (chairman of the subcommittee) presiding.

Senator STEVENSON: The subcommittee will come to order.

OPENING STATEMENT BY SENATOR STEVENSON

Senator STEVENSON. The subcommittee will come to order.

At the time of our hearings in 1977, less than a half a dozen companies were engaged in recombinant DNA research. No breakthroughs leading to commercial products had been announced. No firm had reached the point of taking a recombinant DNA process from the laboratory bench to pilot or commercial production.

Human insulin, growth hormone, interferon, and other products have since been synthesized by genetically engineered bacteria. Genentech and Eli Lilly Co. have NIH approval to scale up to pilot production of insulin and other hormones for testing.

There is greater confidence among scientists that conventional recombinant DNA work, especially with *E. coli* K-12, presents no significant risk to human health. Wholesale revision of the NIH guidelines in 1978 has been followed by selective downgrading of containment requirements; yet, the National Institutes of Health recently extended their oversight to industry by approving proposals to move from the laboratory to production and by recommending standards for large-scale activity. At the instigation of the Occupational Safety and Health Administration, a new interagency committee is considering the need for regulation to protect workers exposed to recombinant DNA materials. So the issue of regulation is not dead. But public attention has turned to the promise of recombinant DNA and other so-called biotechnologies for public health, agricultural productivity, industrial growth, and even for energy production and pollution control.

For several years this committee has studied the state of American technology and its bearing on industrial productivity and the competitiveness of the United States in a highly competitive world market.

We are encouraged by the flow of capital and talent to this promising, high-risk enterprise; but we know from experience that its success is anything but guaranteed. America's industrial oppor-

application of recombinant DNA techniques and will be making recommendations to the larger Federal interagency committee chaired by Dr. Fredrickson. This Industrial Practices Subcommittee allows agencies most concerned with commercial applications the opportunity to discuss their responsibilities and activities. As NIOSH formulates its plans for a review of commercial development, we will be seeking expertise and counsel from interagency group.

In March 1977, Dr. John F. Finklea, former director of NIOSH, made the following recommendations before the Subcommittee on Health and The Environment of the House Committee on Interstate and Foreign Commerce:

"1. Establishment of a central registry of all workers engaged in recombinant DNA research, including the operation and maintenance of laboratories and pilot plants.

"2. Provisions for a program of appropriate medical examinations for such workers prior to placement and periodically thereafter.

"3. Assurance that all workers will be trained to perform their work safely and be adequately informed about the nature of their work and any potential health risks associated with recombinant DNA research.

"4. Adequate labelling and posting in each work area so that workers entering these areas may be reminded of the precautions necessary to protect their health.

"5. Provision to retain health records and all records detailing the configuration and operational history of each research facility.

"6. Mandatory reporting of illness, injury, deaths, and provisions to facilitate medical follow-up of workers engaged or formerly engaged in recombinant DNA research.

"7. Appropriate environmental and workplace monitoring systems to assure that inadvertent exposures to recombinant DNA organisms are not taking place.

We are reviewing these recommendations in light of the continuing work of scientists and the NIH Recombinant DNA Advisory Committee. Finally we will advise OSHA on what should be incorporated in a program to protect workers as new recombinant DNA techniques and approaches move from the research laboratory to commercial application.

Senator STEVENSON. Our next witness is Dr. Donald Fredrickson, Director of the National Institutes of Health.

STATEMENT OF DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH, ACCOMPANIED BY DR. BERNARD TALBOT, SPECIAL ASSISTANT; AND DR. WILLIAM D. GARTLAND, DIRECTOR, NIH OFFICE OF RECOMBINANT DNA ACTIVITIES

Senator STEVENSON. Please proceed, sir.

Dr. FREDRICKSON. Mr. Chairman and Senator Schmitt, it is a pleasure to be back to see you again. I have two people with me I would like to introduce. On your right is Dr. Bernard Talbot, who is my Special Assistant for matters in the area of recombinant DNA; and Dr. William Gartland, on your left, who is Director of the NIH Office of Recombinant DNA Activities.

I have a relatively brief statement, and I should like to read it if I may, Mr. Chairman.

Senator STEVENSON. Very well.

Dr. FREDRICKSON. In this statement, I will briefly cover four topics today: revision of the NIH guidelines for research involving recombinant DNA molecules; risk assessment; the involvement of the private sector with the guidelines; and the Industrial Practices Subcommittee of the Federal Interagency Advisory Committee on Recombinant DNA Research.

The original NIH guidelines, promulgated in 1976, established very stringent containment levels for recombinant DNA experimentation. During the 2½-year period leading to their major revision in December of 1978, a series of scientific and public meetings

demonstrated the existence of a broad consensus that the guidelines were overly restrictive.

The December 1978 revised guidelines lowered the containment levels for many experiments and established new procedures badly needed for the future evolution of the guidelines.

The membership of the NIH Recombinant DNA Advisory Committee, which I shall call the "RAC" throughout my presentation, was broadened to include additional scientific disciplines and lay representatives.

Any proposals for a further change in the guidelines is now published for public comment at least 30 days prior to a quarterly meeting of the RAC, considered by the RAC in public session, and the final decision published in the Federal Register.

The NIH Director has the option of calling for a second period of public comment after the RAC has forwarded a recommendation, and we have done so in one instance.

Using this procedure, modifications in the NIH guidelines have been made essentially every 3 months since December 1978. Some scientists continue to believe that the NIH guidelines are overly restrictive, and other persons believe they are unduly lax.

However, I think it is fair to say that the overwhelming consensus of opinion, as is evident in the votes of the RAC and public comments received, indicates broad support for the revisions which have been made to date.

The complete record of the changes in the guidelines is contained in a series that NIH has maintained from the beginning, "Recombinant DNA Research," and volume 5 has just arrived from the printer's last week, and I am pleased to transmit a copy to you now. This is the complete public record of decisions made by NIH in the development of the guidelines.

I think that the guideline revision has proceeded in an open and systematic way, and we have tried to serve the broad interests of the public—to afford due process in this manner.

Now briefly about "risk assessment." On September 13, 1979, NIH published in the Federal Register its "Plan for a Program To Assess the Risks of Recombinant DNA Research." We have sponsored a series of experiments and meetings to assess risk, including the Falmouth conference of June 1977; the meeting in Ascot in England on viruses in January 1978; and most recently a workshop was held in Pasadena in April of 1980, just mentioned by the previous witnesses.

Even though *E. coli* K-12 is apparently unable to colonize the normal human intestinal tract, the following question was posed in Pasadena:

Were *E. coli* K-12 producing a hormone or other polypeptide from a eukaryotic organism to colonize the intestinal tract, what would be the potential risk either by a direct adverse effect of the hormone or by the elicitation of autoimmunity?

The conclusion of most of those present was that the risks of either of these dangers was minimal. Suggestions for additional experiments were made.

The original NIH guidelines of 1976 said nothing about the private sector. They dealt only with those receiving Federal funds for recombinant DNA research. In the absence of action by other

Federal agencies to apply the guidelines to the private sector, NIH has recently provided a means for industry compliance.

Part VI of the NIH guidelines, called, voluntary compliance, was formally promulgated on January 29, 1980, following its endorsement by the Federal Interagency Advisory Committee on Recombinant DNA Research and by the RAC. Part VI encourages voluntary compliance by the private sector and specifies how NIH will protect proprietary information voluntarily submitted.

The private sector may voluntarily submit the membership of their Institutional Biosafety Committees to NIH, and we will attempt to verify that they meet the requirements of the NIH guidelines.

The guidelines state that all recombinant DNA experiments over 10 liters in volume require prior approval by the Director of NIH. To date, 7 proposals to exceed 10 liters have been recommended for approval by the RAC and have been approved by NIH, followed by a notice of such in the Federal Register.

These seven proposals—all voluntary submissions from two companies, Eli Lilly & Co., and Genentech, Inc.—include attempts at large-scale production of human insulin and growth hormone.

On the recommendation of the RAC, NIH quite recently published in the Federal Register on April 11, 1980, a section entitled, "Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules," a section intended to provide a model against which submissions by those intending large-scale experiments might be measured.

At the most recent—and that was the eleventh—meeting on February 27, 1980, of the Federal Interagency Advisory Committee on Recombinant DNA Research (a committee, Mr. Chairman, which includes members from all agencies within the Federal Government who have an interest in this type of experimentation, whether they be research or regulatory agencies).

An Industrial Practices Subcommittee was established. The charge to this subcommittee was to consider issues of occupational health and other Federal responsibilities attendant upon industrial applications of recombinant DNA technology, and to recommend what steps, if any, should be taken beyond the NIH guidelines.

This Industrial Practices Subcommittee is chaired by Dr. Gilbert Omenn, who then was with OSTP and is now Associate Director of the Office of Management and Budget. It met once in April and will again meet in June with invited representatives of labor and industry. We expect their report to the full committee this autumn.

This concludes my formal testimony, Mr. Chairman. We have much background material which we can supply for the record if you wish. We will be pleased to try and answer any questions you may have.

Senator STEVENSON. Thank you, sir.

The last time we held hearings on this subject, 2½ years ago—you said that it would be wrong for NIH to both promote and regulate this research. I think you acknowledged that you did not have the experience or the legal authority to regulate, but that is precisely what you are doing now, are you not?

Dr. FREDRICKSON. I think we are not regulating, Mr. Chairman—at least we attempt to try to maintain that fine line. We are not a

REMARKS ON THE OCCASION OF
THE FIFTH ANNIVERSARY OF
THE NATIONAL INSTITUTE ON AGING*

by

Donald S. Fredrickson, M.D.**

Dr. Bowers, Director Butler, members of the Council, and all of you, who like I am, are enthusiastic supporters and admirers of this National Institute on Aging. I looked at the printed program this morning, discovered the official title of my remarks and realized that it's time to carry out a determined promise made to myself long ago.

Some of you may have seen, probably will know better than I, the text of a card that the author of "Memoirs of Hecate County" once had published: "Edmund Wilson regrets," it runs, "that he cannot kiss babies, write book reviews, offer blurbs for dust jackets, make speeches, sign autographs," and so forth. So sweeping a rejection slip was all very well for an ego like Wilson's nourished as it was the capacity to parse irregular Russian verbs with Nabokov, and to write so magnificently as he did.

I can't come up to that wallop, but I am going to have my card published to read as follows: "Donald Fredrickson regrets

* Presented at the Lister Hill Auditorium, National Institutes of Health, on May 29, 1980.

** Director, National Institutes of Health, Bethesda, Maryland.

that he cannot provide you with a specific title for the remarks that he has foolishly agreed to make on an occasion many months from now."

Lacking such protection, I find today that I am the victim of a self-inflicted title such as, "An Orphan Finds a Home." It conjures an image of the National Institute on Aging akin to a Norman Rockwell painting of a waif, nose pressed against the window pane. It provides no justice to this youthful figure of an institute that is clearly moving on toward maturity, is in full vigor and deserves no such piteous treatment from me.

The date for this NIA celebration, it seems to me, has been selected like the Queen's birthday, for the convenience of all concerned. Such flexibility is certainly appropriate to the very large number of people who have been in at the creation of this Institute, and who have dedicated to it prodigious amounts of their energies and interests. Senator Eagleton, who I gather we may see this evening, and former Congressman Paul Rogers would likely say that May 31, 1974, the day the President signed the authorizing act, is the true beginning date from which to reckon future anniversaries.

Purists in bureaucratic process would go back to October of '74, when the Institute came into being on paper in a formal way. You members of the Council who are all back here today in reunion would, I suppose, go back to sometime in April '75, when you had your first Council meeting; for in many ways, an Institute doesn't really exist unless the Council says it does. For many of us,

this fifth anniversary will come about in July. It was July 1975 when the Adult Development and the Aging branches and the Gerontology Research Center were separated from their parent Institute, and the Institute on Aging was undeniably here.

I think that latter anniversary, July 1975, does stick in my mind, too, because it was the day that I was sworn in as the eleventh Director of NIH. I remember my Senate confirmation. It eventually required a formal note, but consisted mainly of going around to offices of important people--which of course included a visit to Florence Mahoney's residence. In this tour, I learned from many people their views on biomedical research. Senator Eagleton fixed a gimlet stare and thrust a finger into my mind, so as to leave no doubts about his intentions to see that the next Director of NIH took care of the fledgling Institute on Aging.

Florence Mahoney, of course, was similarly determined. I don't hesitate to single her out in these opening phrases as one who lent much of herself to assure the beginning of this Institute.

When I took the Director's chair, four or five of the Institutes had vacant Directorships. I continue to be extremely grateful to all those who helped me find and convince Bob Butler to be the first Director of the National Institute on Aging, and to guide it during those critical early years. What an extraordinarily good selection that was.

In addition to Bob, there are many others whom I've helped move into the ranks of the Institute or to become interested in its activities. I'm grateful to them, too, for lending their

talents and efforts to the difficult task of starting something new. People like Bob Ringler, and others here today, have created a still too small, but loyal and effective staff for NIA. I remember doing my best to convince Matilda Riley, too, that she must come down and join us, and how delighted I am that she is here. Clearly this Institute has started up in a most encouraging way.

One of the things that Bob Butler and his staff are to be congratulated upon is their quick realization that, being small, they can do much more by closely collaborating with the many other institutes, agencies, and organizations whose interests intersect their own.

Mine is a job requiring a spectrum of interests. Yesterday, I was talking to a reporter who had come to inquire about tenure. There has been speculation in the press -- quite unfounded -- that Secretary Harris and I are at sixes and sevens over some pending legislation. Last week I missed the opening of this beautiful hall in Lister Hill, and thus, my scheduled introduction of Mrs. Harris. At the last moment, I'd been asked to accompany the President to Mount St. Helens. The Secretary noted at the opening that there was no truth to the rumor that Dr. Fredrickson would rather go out and face a live volcano than to see her here. On my return, I sent to Mrs. Harris a bottle of volcanic ash. Tied to it with a blue ribbon was a small note: "Dear Madam Secretary, we can't go on not meeting this way."

These nuances aside, the job of the Director of NIH is a

little like that of the President of Switzerland. The real energies of NIH and its personality is derived from a synthesis of different cantons called Institutes. The Uri, Schweiz, and Unterwald are Cancer, Dental, and Heart. Each of the "cantons" has its own personality, constituency, even dialect. They also have their own budgets, and most are statutory creations tied awkwardly in a greater federation.

Certainly, then, it's not surprising to find that NIA is different from all the other Institutes. It has the usual diversity of concerns and challenges that marks its sisters. NIA also has a history running back to the beginnings of this agency. Gerontology studies began in 1940, long before the Heart Institute, which eventually housed them. Doubtless Nathan Shock will remind you of this today in greater detail.

The primary challenge of NIA is to bring the scientific method to bear on an inevitable phase of life, and on an important part of the human family. To do that, it needs the talents and the interests of scientists of many persuasions, by no means not just biology. No Institute adds so much of that extra dimension -- the social sciences -- to the more quantitative sciences with which NIH is much more familiar.

Another task of consequence to this Institute is to develop a much broader constituency among different kinds of scientists. It has to extend the narrow definition of its own mission, gerontology. We have to stimulate a market of greater talent to subscribe to aging research.

Many of our fellow researchers and practitioners have taken refuge in parochial views about aging, which are years, even centuries, out of date. The laissez-faire attitude that the pace and manifestations of aging are not susceptible to manipulation is still uncomfortably common in scientific and academic communities. It is being challenged by a growing, now generalized, public concern that the average life expectancy is lengthening and that the quality of the last years can be improved by better attention to the early ones.

The forces and the concerns that energized the development of the Institute on Aging are strong, but tend to oppose the focusing upon a few major sectors. Many people understandably, have urgent, personal agendas for NIA. I think a notable accomplishment of the Institute's leadership thus far has been to avoid a debilitating division of effort, while drawing, at the same time, upon the strengths of diversity of public and institutional interest in the problem of aging.

I applaud the special effort that the Institute has made to call the public's attention to the cruel and wasteful tendency to stereotype the aging. They have made a special point of getting the message across to the young, many of whom are isolated by today's living patterns from the older members of their family. Prejudice against, or even callous disregard, of the aging person and process is a unique form of bigotry. It is a way of avoiding a clear vision of what Dr. Butler has felicitously called "our future selves."

The National Institute of Aging has not, I'm glad to say, yielded to the pressures to mount a crash effort for extending the life expectancy tables, no matter what kind of life such added years would bring. I believe that the leaders of the Institute are correct in striving to understand the workings of the biological clock, but choosing not to make a supreme effort to stop it or to turn it back. I think their sensible objective is to improve individual and social adaptation to the inevitable.

I think as we pause briefly now for an anniversary assessment, we do so against the background of three evident certainties. In dealing with the aged, we are engaging with a problem of which each of us some day expects to be a part. In the NIA, we have a promising development of a very powerful instrument for gaining a better understanding of how the interactions of a person and his world change with age. Finally, in achieving that understanding, we will learn not only how to cope with aging, but perhaps we shall also learn how better to enjoy it.

Happy birthday, NIA. I'm proud to be here on this occasion.

WELCOMING REMARKS*

by

Donald S. Fredrickson, M.D.**

I am aware that the RAC has engaged in much discussion of the task it has accepted to review applications involving proprietary information, usually submitted by private concerns not supported by Federal funds in voluntary compliance with the NIH Guidelines. Particularly, some members of the RAC have chafed under the need for examination and approval of scale-up operations in industry, a result of the 10-liter limit in the Guidelines. Certainly most members find the task onerous and not a few still find distasteful the scientific review of information subject to safeguards including criminal penalties for violation. Some members of the RAC also are of the opinion:

1. that the task involves judgments about apparatus for physical containment which do not rest upon the same experience and training useful for decisions about molecular biology and other aspects of recombinant technology; or
2. that when the judgments about physical containment require site inspections in industry, such visits belie the insistence of NIH, and its Director, that this agency eschews a regulatory role; and, finally,

* Presented at the meeting of the Recombinant Advisory Committee at NIH on June 5, 1980.

** Director, National Institutes of Health, Bethesda, MD.

3. that there are several RAC members who regard consideration of any part of an application from the private sector, perhaps even any proprietary data, as befitting only a regulatory agency, which NIH is not.

I am grateful to all the members of the RAC, whatever their views on this subject, for subordinating their feelings to the extent that they have continued to carry out these important duties. In so doing, they have made it possible for all users of recombinant technology in the U.S.A. to do so under two important conditions that obtain in nearly all other advanced countries of the world. These are:

- (1) the determination of appropriate procedures by a single national body, responsible for interpreting and developing uniform national guidelines, and
- (2) the regulation of a rapidly evolving science without passage of special statutes, avoiding inflexibility often attendant upon such legislation.

These important conditions are among those necessary for maintenance of parity among the nations for safe use of this technology and access to its benefits. It is essential that the RAC, whose deliberations affect of the course of this field of science throughout so much of the world, not alter these conditions by precipitous changes in its procedures.

Nevertheless, I am sympathetic to this malaise of the RAC. We must try to relieve it -- and to move NIH back from what some see as a position on the brink of regulatory involvement. In

thinking about such relief, I note especially the rising interests of OSHA and NIOSH in ascertaining any threats to workers inherent in industrial scale-ups. FDA and other regulatory agencies have also begun to test their reflexes in a similar way. FDA sponsored here this week a useful meeting on industrial application of recombination for production of biologics.

It is appropriate that these agencies begin to consider their mandates as industrial use of recombinant techniques grows. One of the earliest tasks of the IAC was an analysis of the authorities of the regulatory agencies in this area. The results indicated that no single agency had clear authority over laboratory research, but there obviously were appropriate roles for such agencies in the oversight and regulation of industrial-scale use of recombinant methodologies. All the regulatory agencies also have continuously been kept fully informed of the activities concerning the NIH Guidelines, through their membership on the Inter-agency Committee (IAC), and through their liaison membership on the RAC.

At the same time, it should be stated here with candor that no Federal regulatory agency presently has anything like the in-house competence to perform -- for industrial applications -- all of the present tasks of the RAC. Development of such competence will require time and expense, and it would not arise suddenly upon the passage of any statute. Furthermore, we are still at a stage where the creation of more than one RAC in this country -- one for industry, one for non-profit research -- would be inefficient and destroy the unity of information-sharing and decision-making about

the many aspects of handling recombinant DNA activities that facilitate appropriate evolution of guidelines.

It is, however, apparent that in taking any actions appearing to validate physical containment on an industrial scale, the NIH also has insufficient in-house competence, and, like the RAC, must rely on consultants. In these determinations a regulatory agency like OSHA, or its research partner, NIOSH, can use consultants as effectively as can NIH, and may have more staff competence. Such judgments can more appropriately be carried out by them, especially when they are related to a regulatory mission.

From these considerations, I believe that the RAC should consider at least two options as it deliberates upon its procedures for handling industrial or private requests:

- (1) to continue as it is until more experience dictates some new mode. Here keep in mind that an Industrial Uses Subcommittee of the IAC is actively studying the problem and will report to the RAC in the fall.
- (2) to restrict its review and decisions to questions concerning biology and related issues of laboratory containment; and when physical containment for large scale use is the issue, to judge only whether the specified P-LS level is appropriate (referring to the model designations in the April 11, 1980 Federal Register). The regulatory agencies will be fully apprised of such actions. They can make on-site evaluations if they deem them to be appropriate to their regulatory mandate.

With regard to the second option, I would note here that past actions of the RAC have included the insertion of a provision for visits by an NIH designated person to industrial facilities that have been the subject of a RAC decision. If such visits are for purposes of correlating scientific information relevant to the duties of the RAC, they would seem to me to be still appropriate. Inspections for regulatory purposes shall be carried out by OSHA/NIOSH or other regulatory agencies having relevant authority.

Finally, let me emphasize that it would not be appropriate for the RAC to decide, in exasperation, that it would like to avoid handling any proprietary data. The patenting of biological processes and systems by non-profit institutions and their staff members is now both accepted and common. From time-to-time such material will have to be evaluated by the RAC in pursuit of its duties.

I welcome the opportunity to participate in discussion of this matter to the extent that my presence will be useful.

(Announcement of Mr. Thornton's appointment as
the new Chairman of the RAC.)

HEALTH SCIENCE: THE STRUGGLE FOR HOMEOSTASIS*

by

Donald S. Fredrickson, M.D.**

Introduction

Twenty-nine years ago this week I appeared as an endocrinologist on a dingy stage in Atlantic City and defended the first abstract of my career. After the last slide the questioners rose one by one, probing for a fatal thrust. I could see that Endocrinology was going to be a very competitive game.

So I moved over the border into a less populous territory called Metabolism. Unlike Endocrinology, an established land where glandular failures permitted both research and remunerative medical specialization, Metabolism promised little visible means of support. Fortunately for me, however, the newly discovered plasma lipoproteins in which I was interested were soon suspected of causing Western man's most common fatal disease. Slowly, Metabolism, too, became a more inhabited and respectable place.

Now, accepted back in the fold for a day, I still feel like an endocrinologist manque, for I've come to

* Presented at the Endocrine Society Annual Meeting, Sheraton Washington Hotel, June 18, 1980.

** Director, National Institutes of Health, Bethesda, Maryland.

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talk about the Political Economy of Science. Because I'm confining my remarks to the health sciences, I've presumed to cast my subject in metabolic or physiological terms.

Scientific inquiry is a demanding discipline and the modern systems created to foster it have grown increasingly complex. Claude Bernard, patron saint of internal secretions and thus of Endocrinology, instinctively understood complex organisms. They have, he noted, a stable milieu interieur which affords them a characteristic freedom and independence. The resulting vie constante is a much more dependable state than the vie oscillante of organisms lower on the evolutionary scale.

Science is an organism high on the scale of social evolution. Its vitality is dependent upon relative constancy and predictability of its internal conditions. The effectiveness of so creative and cognitive a vocation, with its incessant demand for replenishment of the pool of participants, requires stability. Thus the mechanisms of regulation that keep the system in balance need frequent attention.

It was Walter Cannon who had the word for the equilibria or steady states maintained by coordinated physiological processes. He called them Homeostasis, meaning " . . . a condition which may vary, but which

is relatively constant." Cannon went on to observe that the means for preserving a stable internal economy in highly evolved animals might present some general principles for establishment and control of steady states in even social or industrial organizations suffering from "distressing perturbations."

The homeostasis of a substantial fraction of the biomedical research in the world is mediated through the National Institutes of Health. The semipermeable outer membrane of this institution has one face in contact with a milieu exterieur from which comes not only essential nutrients but a high concentration of other political, economic, and social ingredients. Organisms dependent on this medium are threatened by its oscillatory character and frequently low pH. An important tidal force in this milieu exterieur is one having, in normal times, a period of 12 lunar months. It is known as the Appropriations Cycle. I offer some instruction on this vital mechanism by recitation of a little recent history.

The hearings on the fiscal 1981 appropriations for the National Institutes of Health began according to form on a day in February 1980. On the Senate side of the Capitol, in the elegant quarters of the Senate Appropriations Committee, the numerous Directors of NIH -- its three Bureaus, nine Institutes, and three other units that get separate annual appropriations --

gathered for two days with members of the Subcommittee on Labor, Health, Education, and Welfare -- powerful citizens whose places at the baize-covered conference table are each engraved on brass plates at the rim.

Two weeks after the Senate hearings ended, and a few days before the hearings of the House of Representatives began, the first of the "occasional pieces" appeared in the Sunday Washington Post. (First slide, please.) A reporter had chosen the NIH budget as a vehicle to lead readers through the subtleties of the complex appropriations process.

On February 26, the second round of the proceedings began in the Rayburn Building, before the House Subcommittee on Appropriations for Labor and Health. On eight separate days thereafter, we answered questions from the Chairman and from the six other Democratic and three Republican members of the Subcommittee variously in attendance. Periodically the Post provided further program notes on the participants and proceedings.

At the conclusion, the Chairman observed in his courtly fashion, "We've made a mighty fine record, Doctor. This has been a good hearing."

Yes, as hearings go, we had done well; but things were highly abnormal. The Chairman's last question, to be answered for the record, was "How would you reduce

your budget by \$300 million? Where would you take your cuts?" Moreover, a weekend before, several of us had answered an unprecedented early-morning summons from the Administration. We were asked to describe how we would distribute an even greater reduction, one spread over both the present fiscal year (1980) and the next.

Concerned by a rapidly rising inflation rate and declines in other economic indicators, the President had felt compelled to take stringent cuts in Federal spending. The Congress shared his concerns. During the House hearings, members inquired about the possible effects on biomedical research of other experimental formulas for austerity. Then the Congress learned that it had exceeded its own budget ceilings. Lengthy caucuses and consultations ensued, within and across party lines and in the presence, and the absence, of the Executive Branch. The President then announced his decision to reduce drastically the outlays provided by his budget for fiscal '81.

February has nearly become July. The final outcome of proposed rescissions and reductions is still awaited. So far, the worst predictions of reduction in Federal spending for biomedical research have not been realized. Yet the search for homeostasis is entering a new and important phase. New mechanisms for maintaining the milieu interieur are evolving. Some features suggest a return to earlier periods in the unusual history of NIH.

The agency began before the turn of the century (1887) as a very modest public health laboratory on Staten Island. It eventually became the National Institute of Health (1930) and was relocated in 1938 in Bethesda, Maryland.

The metamorphosis to something more than an intramural laboratory benefited from the enthusiasm for peacetime continuation of Federal support of health research launched during World War II. By 1948 NIH had become plural -- the National Institutes of Health -- and the aggregate was on its way to becoming the staunchest supporter and conductor of research in medicine and the life sciences that the world has seen -- or may ever see again, depending on the fortunes of the American economy in the years ahead.

This slide has been concocted to show the growth curve of the NIH appropriations from 1945 to the present. It is plotted, in current dollars, on a semi-logarithmic scale.

Although the early dramatic rate of growth in NIH had declined by 1962, appropriations of some Institutes have continued to expand selectively. The fiscal '79 appropriation for all NIH was \$3.2 billion. From the signs alluded to above, it is conceivable that this appropriation may have set a high water mark in purchasing power. In constant (1969) dollars, it was

equivalent to \$1.6 billion, compared with \$1.1 billion in '69. The 1980 appropriation and the President's '81 budget will permit less support of research than in 1979.

Certainly America has been bullish about health science in the last quarter-century. Its example has inspired other affluent nations to behave similarly, if on a lesser scale. The resulting expansion of knowledge about living things, including man, has been truly spectacular by nearly everyone's reckoning. The associated improvements in both length and quality of human life must be at least partially credited to these intellectual achievements. Few would put bounds on the potential future growth of knowledge or the conquest of diseases through continued scientific research.

A few months ago, Sidney Ingbar came to NIH to describe the explorations that he, as Chairman, and an Advisory Committee of fourteen other scientists had made along the vast terra incognita beyond the present frontier of endocrinology. We were all immensely impressed by the thoughtful nature of this survey, and the potential for human benefit now visible or imaginable.

It is awesome to contemplate that the known hormones now number more than a hundred. It is also sobering to think how resistant to capture is a complete and precise understanding of their mechanisms

of action. I mean this not as a criticism, but an observation upon the great distance we have yet to travel. We, or future generations, will get there, of course. The limiting rate will be set by the operating capacity of the system -- i.e., the numbers of scientists and laboratories actively engaged.

The growth and development of the health sciences, and of medicine, are partially reflected in the evolutionary history of NIH. In the next slide, the years between 1945 and the present are divided into four epochs. The fanciful designations and arbitrary limits of these eras need not distract us from some instructive inferences.

The extramural dimension of NIH actually began with the creation of the National Cancer Institute (NCI) in 1937. NCI quickly made some of its funds available to non-Federal scientists in the form of "grants-in-aid." But what I call here the Classical decade of NIH began in 1944, when the statutory genie that has since provided the basic authorities for NIH research and training was created with the enactment of Section 301 (Title III) of the Public Health Service Act. The Division of Research Grants was established in 1946 to process applications for grants and to oversee development of a two-tiered system for their review by scientific peers. In 1948 the Cancer Institute was joined by Heart and Dental. Before the

end of that same year, 1,000 grants were in force, about one-third of them for cancer research.

By 1950 an apparatus for scientific inquiry was being vigorously pulled together. The scale was to be American; a century and a half of indifference would be made up in optimism and generosity. At this time, an important change occurred in the orientation of NIH which dominates it even today: the shift in organization from disciplinary to categorical -- that is, by disease or organ system.

For example, the Experimental Biology and Medicine Institute became the National Institute of Arthritis and Metabolic Diseases, a title which has subsequently undergone further adumbration as aficionados of other diseases have made it a focus of their attentions.

As an aside of interest to endocrinologists, we should note that today the NIAMDD -- having also acquired jurisdiction over digestive diseases -- is the world's single largest source of support for research in endocrinology. (Next slide.) From several surveys of the major American outlets for scientific papers on endocrinology we have learned that NIH was cited as a source of support in half of the papers. NIAMDD loomed larger by half over the next largest Institute supporter.

NIAMDD, the Cancer Institute, the National Heart, Lung, and Blood Institute, and the Institute for General Medical Sciences are presently the four biggest supporters of research project grants. NIGMS is a descendant of the Division of General Medical Sciences, which was created in 1958 to offset a categorical emphasis that was beginning to threaten adequate support of the basic disciplines.

In the Classical period of NIH history (next slide, please), the traditional project grant (later coded R01) was the quintessential mode of doing business. The grants were small. The average cost of each of the 1,500 NIH grants in force in 1950 was \$8,900, and the maximum overhead collected by the institution was 8 percent of the total costs. The best ideas were given financial support, and the scientist was left alone after passing the review on the merits of the proposal. It was a laissez-faire period, and accounting was mainly by gentlemen's agreement. But it was a Puritan or Fundamentalist period, too, in the sense that "program relevance" was muted if the science was judged to be excellent. Big projects, the hot pursuit of the quick cure, got a cold reception from the "peers" who, then as now, are the core of the quality control on NIH purchases of research proposals to be supported. (Next slide.)

In 1979 the average R01 was budgeted at \$79,000. Compared with the average R01 of \$8,900 in 1950, the cost of R01s has risen faster than inflation. Research has grown more costly to do.

The "unit of research" that is embodied by the 1980 model R01 now coming off the Council approval lines employs about three people, provides around \$42,000 in salaries and other direct personnel costs, and permits \$14,000 to go for purchase of equipment, supplies, and services. It will also bring to its home institution an average of \$24,000 in indirect costs. The average grant is given for a little over three years. This means the principal investigator must finish his application for renewal near the end of the second year. Today's PI has a half-life of about five years in the system. In Classical times, they lasted three times longer.

The second decade of NIH (next slide) -- a Renaissance period (1955-1965) -- was a time of rapid growth in NIH and of new institutional forms. The NIH appropriation more than doubled between 1956 and 1957. A concern for institutions became manifest in the creation of general research support grants (1960). Likewise, an awareness of the need for new laboratories was expressed in matching funds for construction, reaching a peak of \$64 million in 1965. Contracts had been used sparingly before, but during

this period targeted support grew rapidly. Contract R&D rose from \$4 million in 1957 to \$46 million in 1965.

The research program project grant (P01) was announced with some fanfare in 1962. The first such grant, however, was doubtless awarded long before that, in recognition of differences in the way individual scientists prefer to work. Some wish to be alone, some flourish in troupes. Nobel Laureates are found at both ends of the scale. (Next slide.)

The program project grant supports a number of professional scientists and their work on a central theme or problem. As in the R01, one investigator is the principal. The P01 -- the model for the first "centers" and for the latter-day "master grants" being tried by NSF -- has always been viewed with ambivalence. There are gifted team leaders whose work is best supported in this way. Moreover, the support of a large laboratory (or small department) can greatly reduce the accounting problems attendant upon fragmentation of support into numerous small grants with narrow categorical objectives.

The negative aspects of the P01 are the possibility of overextending too far the shadow of an excessively entrepreneurial "PJ," or a masking of mediocre pieces supported within the whole. The

vulnerability to sudden extinction of the many whose support derives from a single grant also makes the P01 a riskier bet in today's highly competitive bidding for support of research ideas.

The budgeted cost of the average P01 was \$583,000 in fiscal '79. One P01 thus bumps more than six R01s below the payline. Thus the balance between R01s and P01s must be watched carefully in maintaining the sizable enterprise represented by project grants. In fiscal '70, about 10,000 research project grants (R01s and P01s) were in force. The percentage of grants that were R01s (94 percent) was fairly steady through the 1970s. (Next slide.)

In fiscal '79, the total number of grants being supported at year's end was 14,600*. Three percent were the king-size P01s. The proportion of research project grant funds going to R01s in 1979 (80 percent) was slightly higher than in 1970. The two kinds of grants, R01s and P01s, have been increasing in cost at about the same rate over the last 10 years.

Concern for the stability of the capacity to support sufficient R01 and P01 grants grew during the sixties. It was not so much engendered by the declining rate of growth in NIH after 1961, for modest growth was still steady until about 1969. Rather, it

* Excludes supplements.

was the erratic, asymmetrical growth, and sometimes the bizarre course of both organization and budget, that characterized the decade from 1965 to '75. There is ample justification for labeling this epoch a Baroque period in NIH history. (Next slide.)

Here are some of the features of the times. The National Institute of Mental Health marched away to become a separate research cum service organization in 1967**. Special interests (members of the protean movement called the Disease-of-the-Month Club) gained satisfaction in the creation of new Institutes (Eye and Aging) or mandated programs (sickle cell disease, Cooley's anemia, sudden infant death, diabetes, communicative disorders, etc.). Some of these initiatives sought to earmark a greater share of the funds available for R01 and P01 grants; often they helped increase those funds in a general way. Many of the disease initiatives included the urge to create clusters of categorical (disease-dedicated) research centers. Between 1970 and 1975, research center grant support grew from \$98 to \$244 million.

The Granddaddy of all disease initiatives was the National Cancer Act of 1971. It was accompanied by a fourfold rise in the budget of the National Cancer Institute between 1970-1975. The largest proportion of

** The programs that have been transferred out of NIH are not represented in the figures.

these funds was not allocated to research project grants. The amounts going to "collaborative research" (largely contract-supported) raised anew the old questions of program balance and whether enough untargeted research was being maintained.

By 1975 the Baroque began to cool. Massive experiments to convert NIH into a supervisor of Regional Medical Programs or of Health Manpower Education (a \$587 million expenditure in 1973***) had come and gone. The schism of NIH threatened by the Cancer Program had been avoided, but the use of massive contracts was exciting the oversight of Congressional committees. A taste for an abundance of project grants was returning. Training and general research support had become bones of contention between the Administration and the Congress, and support for both was declining. (Next slide.)

The Contemporary period, from about 1975 to the present, has been marked by certain strong initiatives of its own. Some have been related to readjustment of the boundaries of NIH. A confusion of responsibilities became acute in the mid-70s, having diverse origins in concern over technology and cost containment and in diffuse irritation with science, as with all elite institutions. New approaches were taken in the

*** Including construction grants.

evaluation of biomedical technology and the assuagement of anxieties arising from some scientific inventions. At the same time it became necessary to take steps to prevent regulatory, service, or excessive advocacy missions from damaging the objective setting and sharpness of the scientific instrument which NIH preeminently maintains in the interest of public health. (Next slide -- blue, plain.)

The Contemporary period has also seen the first real confrontations of NIH with serious budget constraints. The shrinking of budgets due to inflation, the increasingly tenuous support for training and the research environment, the funding of expensive clinical trials, and the exploitation of enormously expanding opportunities in many fields simultaneously have all seemed to converge at the midpoint in this fourth decade of NIH.

At NIH we have been anticipating austerity and its attendant strain on the mechanisms for homeostasis -- preparing for it, in fact, for several years, back in times when gloom was suppressed because it might become a self-fulfilling prophecy. (Next slide -- budget v. approp.)

For many years the mode of change in the annual Federal outlays that are provided for biomedical and behavioral research in the NIH budget has tended toward

a stereotype: measured frugality of the Executive calculated to balance the generosity of the Legislature. The average Congressional increase in the appropriation over the Presidential request has been 10 percent in the past 10 years. To those of us who are appointed observers of the system, however, it became progressively evident that such oscillations might eventually be completely dampened by appropriations ceilings imposed by the Congress on itself. The horizons of proposal and disposal of the NIH budget were converging. Over the years 1975-77, NIH superimposed a new matrix for analysis upon its resource allocations, intensified the integration of forward planning, and quietly added life-boat drills in budget reduction.

In 1978 the Administration sent up a budget requesting the previous year's level for NIH. In defiance of its then experimental, nonbinding budget ceiling, Congress pointedly overcorrected for inflation in its fiscal '79 appropriation for health research. The gap between the Branches was widening, like a fault before some cataclysmic collapse. (Next slide -- Califano.)

The Secretary of HEW, made aware that a crucial corner of his vast budget contained nearly half of the world's non-industrial support for the biomedical sciences, ordered a Department-wide, long-range plan for health research. Nine-tenths of the Department's

\$4 billion for this purpose being the responsibility of NIH, this agency led the effort, but the planning involved all HEW health agencies. In October 1978 hundreds of citizens were invited to Bethesda for a two-day conference. Although lampooned as "peculiarly American," this festival yielded a harvest of principles to guide the Government in using public funds for the health sciences.

The principles had not yet been distilled and distributed when the Congress, this time with pain, increased by 8 percent the NIH budget for fiscal '80. (next slide -- budget v. approp.) The Administration had proposed a level budget in the face of 9 percent inflation. (Next slide -- pink.)

During 1979 several intensive negotiations, involving pains and strains of their own, proceeded apace. The NIH Institutes, seeking formulas that both Executive and Legislative Branches might jointly embrace for inducing stability in research funding, finally agreed upon a plan. As a first priority in developing the fiscal '81 budget, NIH would request sufficient funds to put a floor under the power to fund research project grants, and would seek to gain some commitment to this objective from both Executive and Legislative patrons for a period of at least five years.

In a second round of negotiations at the Department, the HEW research agencies sought new ecumenical union around a few interagency initiatives designed to convert the research funding principles into practice. The Alcohol, Drug Abuse, and Mental Health Administration joined NIH in seeking predictable purchasing power for research project grants.

The "stabilization" initiative became the first of several to survive the second phase of planning. It had two important practical features. One, it gave a strong priority to research project grants in reshaping the budget to fit any particular ceiling. Two, it converted this priority into an easily understood and remembered target -- a minimum number of new (or competing renewal) grants to be funded each year. The annual goal selected by NIH was 5,000 (Next slide -- total v. competing).

This minimum goal represented a compromise between the high number of competing grants (almost 6,000) awarded during the vintage fiscal year '79 and the projected number for 1980. The future budget projections attempted to compensate for an 8-to-10 percent annual inflation in the cost of grants.

The "5,000 grants" survived the hot summer in Washington -- even the interruption of the budget development by a change of Secretaries. Lost in the

budget's preliminary tour through the astringent vapors of the CMB, the 5,000 were dramatically restored in appeals by the Department. The President's budget unveiled in January 1980 proposed a 4.4 percent rise, most of it earmarked to permit the funding of the new grants. It was the largest increase in a President's budget over the previous NIH appropriation in the last eight years.

In the 60 days between the presentation of that budget and the emergence of its replacement shrunk to effect economies, the 5,000 grants disappeared from the screen on several occasions. The Washington newsletters referred to expected cuts of some \$350 million in the NIH budget. (Next slide -- budget v. approp.) Cuts of such magnitude would spell a capacity for funding about 3,000 new grants in fiscal '81 -- half the number awarded in '79. The large community of scientists supported by NIH grants coming up for renewal in '81 -- and those for new projects seeking initiation -- would receive a chilling reception. There were many alarms and excursions behind the scenes.

On March 31 the President released his revised budget for fiscal '81. Of the \$550 million stripped from the Public Health Service budget, NIH lost \$90 million. The salvage carried a stipulation: "fund the 5,000 grants." The "5,000 grants" in the story of the NIH budget for fiscal '81 refers to the investigator-

initiated research project grants -- R0ls, or traditional grants, and P0ls, or program project grants. (Lights, please.)

This landmark restoration, has yet to be placed in perspective by further Congressional actions this year. The willingness of the Administration to signal to the Congress that both should assume a long-range commitment to homeostasis of the health sciences is of great moment in a time of economic uncertainty. It should not be interpreted as implying that anyone believes the simple guarantee of a number of project grants is an adequate mechanism for homeostasis of the complex system established for health science. The support of project grants has been selected as the most important priority for a first step in assuring stability.

In the President's revised 1981 Budget, other mechanisms of support for research and training have been trimmed to maintain the project grant program. Thus, training support, centers, intramural research, the National Library of Medicine, R&D contracts, clinical trials, and other applications of research will inevitably share the effects of inflation.

None of these other forms of research support can bear much further reduction in future years in order to guarantee the projected annual minimum of competing

grants. New initiatives to stabilize support at predictable levels for these other mechanisms will be required to maintain the milieu interieur of health science. The struggle for homeostasis -- as with the adaptive development in all organisms -- is unending.

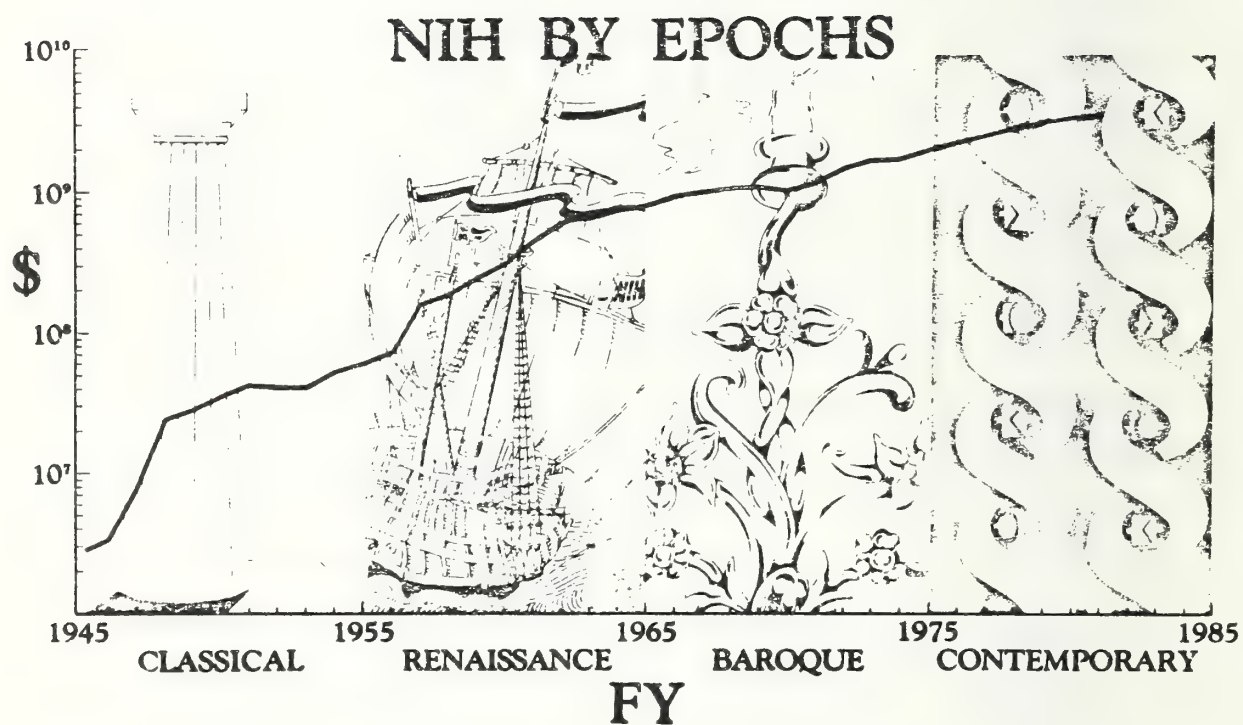
For so complex an organism, a single turn of the appropriations cycle can encompass only an increment of adaptation. This year I have been particularly concerned that our stabilization objectives be recognized by scientists as necessarily phasic and necessarily incomplete.

One needs to be reassured. It is comforting, therefore, to read in the Ingbar Report that the Advisory Committee unanimously and strongly recommends the following:

Increased allocations should be directed mainly to the support of individual investigator-initiated research grants, the area in which the most urgent and immediate need is perceived to exist.

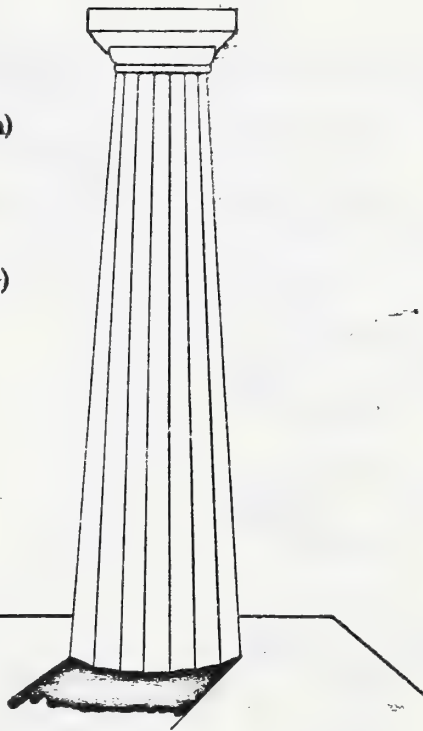
Right on, Endocrinology! We agree to the first step toward homeostasis.

(I see, by the way, that Endocrinology has annexed Metabolism in the Ingbar Report. I guess that means that today, as an old exile, I've come home again!)

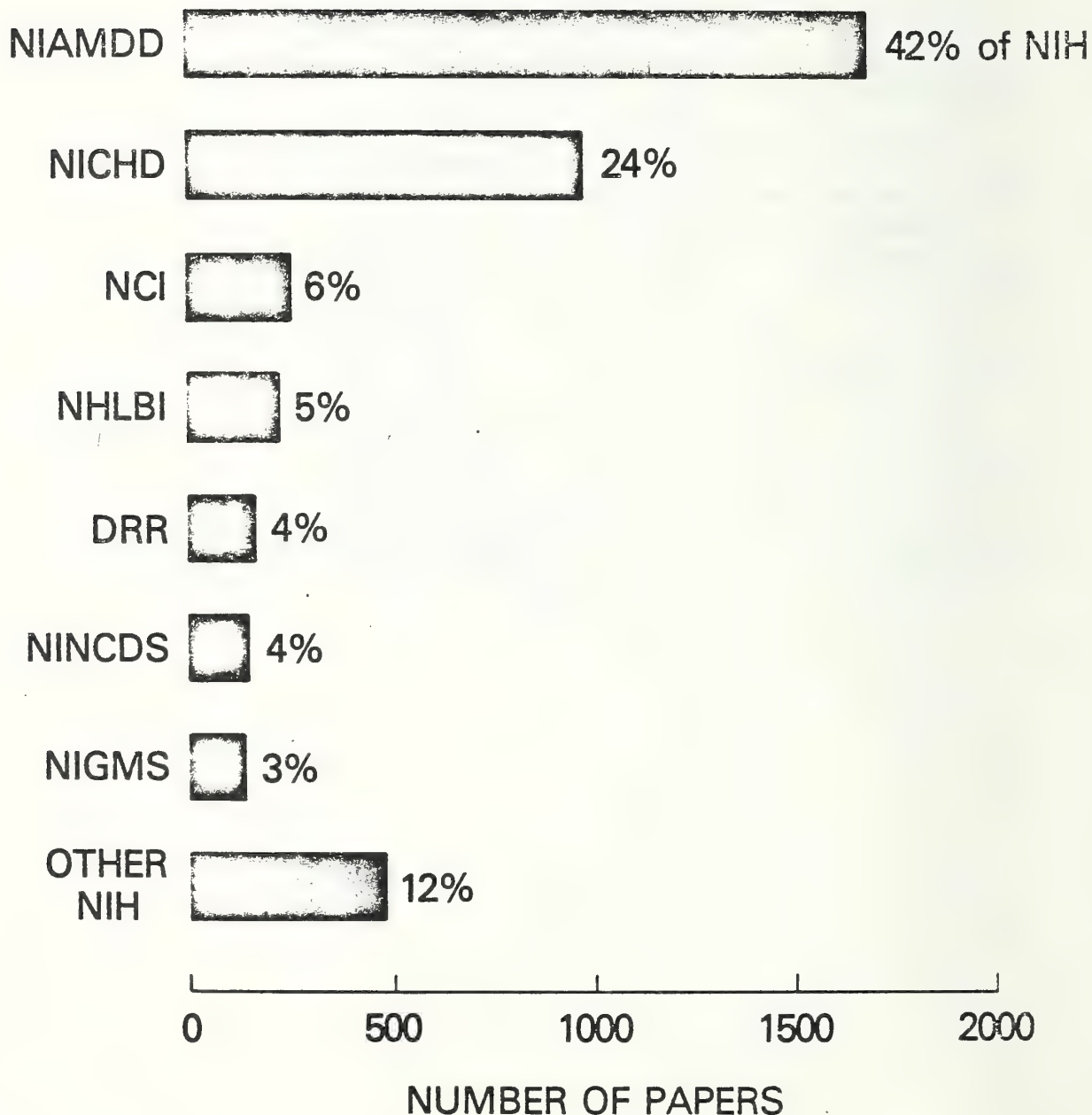


CLASSICAL 1945-55

- Laissez-faire approach (Age of Faith)
- Traditional grants (RO1)
- Central mechanism for grant management (DRG)
- Multidisciplinary fellowships (DRG)
- Orientation shifts from disciplines to diseases



PAPERS IN ENDOCRINOLOGY
SUPPORTED BY NIH
(1970-1976 combined)



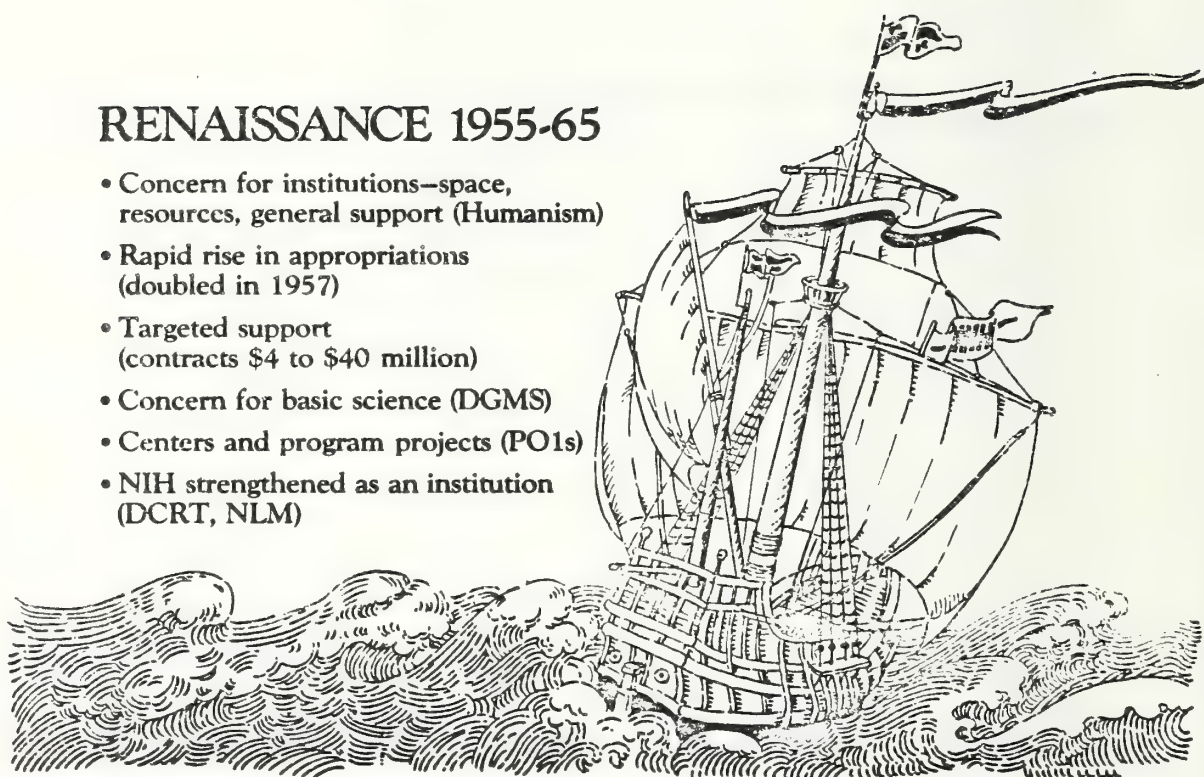
THE NIH RO1 GRANT (FY 1979)

<u>Budget category</u>	<u>Average grant (thousands)</u>	<u>Percent</u>
Direct costs	\$56.6	71%
Personnel	38.6	49
Supplies	8.8	11
Equipment	3.6	5
Travel	0.9	1
Purchased services	0.8	1
Hosp. & outpatient	0.1	-
All other	3.8	4
Indirect costs	<u>22.5</u>	<u>29</u>
Total	\$79.1	100%

Budgeted amount--\$1.1 million
 Number of awards--14,210
 Estimated no. of PIs--12,030
 Number of institutions--716

RENAISSANCE 1955-65

- Concern for institutions—space, resources, general support (Humanism)
- Rapid rise in appropriations (doubled in 1957)
- Targeted support (contracts \$4 to \$40 million)
- Concern for basic science (DGMS)
- Centers and program projects (PO1s)
- NIH strengthened as an institution (DCRT, NLM)



THE NIH P01 GRANT (FY 1979)

<u>Budget category</u>	<u>Average grant (thousands)</u>	<u>Percent</u>
Direct costs	\$427	73%
Personnel	270	46
Supplies	52	9
Equipment	28	5
Purchased services	23	4
Hosp. & outpatient	16	3
Travel	5	1
All other	33	5
Indirect costs	156	27
Total	\$583	100%

Budgeted amount--\$258 million

Number of awards--443

Estimated no. of PIs--400

Number of institutions--146

R01 AND P01 GRANTS BY INSTITUTE, FY 1979
(Dollars in Millions)

<u>Institute</u>	<u>R01</u>	<u>P01</u>	<u>r</u>
Total	<u>\$1,118.6</u>	<u>\$260.1</u>	<u>4.3</u>
NIA	22.4	9.9	2.3
NIAID	93.5	11.5	8.1
NIAMDD	173.4	14.3	12.1
NCI	191.3	93.2	2.1
NICHD	84.9	22.4	3.8
NIDR	22.6	3.1	7.3
NIEHS	19.7	8.0	2.5
NEI	70.5	-	-
NIGMS	175.3	13.4	13.1
NHLBI	177.5	69.2	2.6
NINCDS	87.5	15.0	5.8

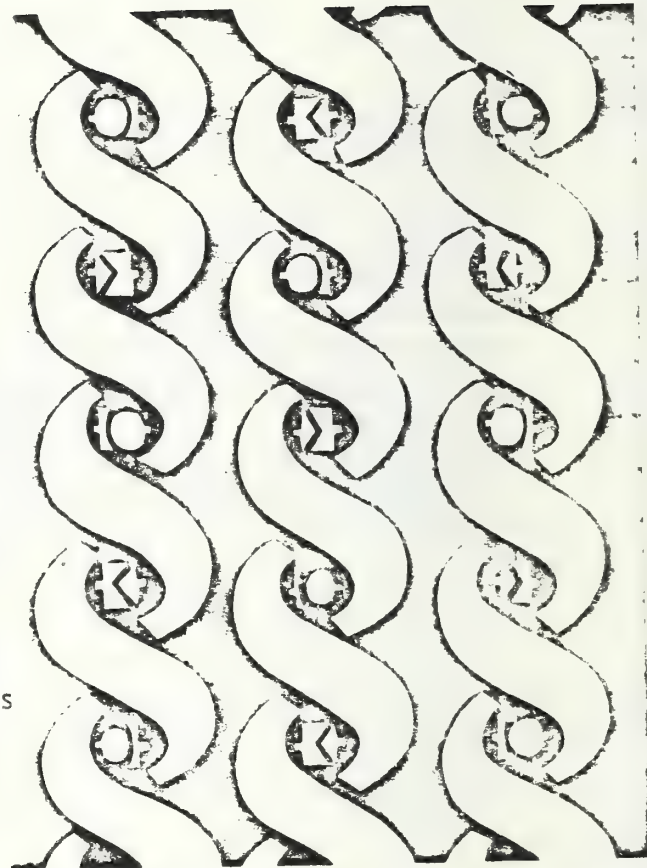
BAROQUE 1965-75

- Slower, bizarre expansion
- NIMH, disease control, and technology transfer (RMP) out
- Responsibility for nation's health manpower (\$520 million in 1973)
- Disease-of-the-month, highlighted by Cancer Act of 1971
- OMB at odds with scientific community on policy—research training and general support



CONTEMPORARY
1975-85

- Level, then shrinking budgets due to inflation
- 1979 peak in constant dollars
- Indirect costs continue to rise
- Period marked by strong initiatives
 - ...technology consensus and transfer
 - ...HEW-wide research planning
 - ...strong program budgeting
 - ...effort to stabilize research grants



HISTORY OF CONGRESSIONAL ACTION ON
 BUDGET REQUESTS FOR NIH
 FY 1969 - 1980
 (Millions of Dollars)

<u>Fiscal year</u>	<u>President's budget</u>	<u>Appropriation</u>	
		<u>Current \$</u>	<u>Constant \$</u>
1969	\$1,131	\$1,118	\$1,118
1970	1,084	1,061	998
1971	1,119	1,213	1,078
1972	1,360	1,506	1,276
1973	1,620	1,763	1,425
1974	1,577	1,790	1,362
1975	1,835	2,093	1,437
1976	1,980	2,302	1,471
1977	2,165	2,544	1,506
1978	2,596	2,843	1,566
1979	2,885	3,190	1,623
1980	3,186	3,388	1,580

NUMBER OF NIH RESEARCH PROJECT GRANTS
FY 1970-1981

<u>FY</u>	<u>Total</u>	<u>Competing</u>
1970	9,688	2,580
1971	9,313	2,691
1972	9,848	3,625
1973	9,575	2,592
1974	11,162	4,540
1975	11,535	4,663
1976	11,889	3,464
1977	12,022	3,840
1978	13,069	5,200
1979	15,335	5,944
1980*	16,200	4,700
1981*	16,500	5,000

*Estimated.

REMARKS 1/

by

Donald S. Fredrickson, M.D.2/

Good morning. It's my pleasure to welcome you to an occasion of some joy. It is the sharing in a process of self-renewal which is important to all living organisms. Here at NIH we share a self-perception that we are a special kind of living organism--one of the most fragile kinds. We're not a government agency. We're a university. And I think that we really are, by almost any definition. If you take Carlyle's view "that a true university is a pile of books," we've a million and a half volumes stacked in the complex where we're sitting this morning. Or if a university is a community of scholars, we have only to stroll on this campus to see more than a thousand at work. There are even more, for the limits of this particular university are not just some 300 acres. There are really almost 100,000 scholars over the globe whose search for reality and for truth is lighted by lamps whose fuel is renewed periodically from here. NIH is a university even in the cosmic sense. And if a university be a collection of deans, then a more than adequate number of replicas of these are crammed into Senator Hill's sumptuous parlor here this morning.

As certain as we have been of the validity of our claim to being a university, as frequent have been our claims to a lack of

1/ For presentation at the Swearing-in Ceremony of Dr. Vincent DeVita as Director of the National Cancer Institute, 10:30 a.m., August 8, 1980, Lister Hill Auditorium, NIH, Bethesda, Maryland

2/ Director, National Institutes of Health

some of the most ordinary scholastic amenities. Until the early seventies the only academic processions we had were the annual progression of Institute Directors before the appropriations committees early in the spring semester. An Act of Congress in 1971 improved upon this bare cupboard of social occasions in the sense of elevating two among the numerous directors to Presidential appointments and thus entitling us to share infrequently in more ceremonious swearings-in.

There is some cost to these new amenities, of course. We have to lose a director first to swear a new one in; but that, too, is part of the necessary process of renewal. The National Cancer Act of 1971 added more than amenities to a part of NIH which began in 1937, when in his second term Franklin D. Roosevelt signed the National Cancer Institute Act and created the first of the "categorical" colleges in this university. The bill setting up the National Cancer Institute was sponsored by every senator and passed unanimously by the House. And today that Institute is the origin of half of all the support around the world for the search to conquer the deadly secrets of the disease that excites so much fear and anxiety among people everywhere.

We're now in the fifth decade of the NCI suzerainty over research in neoplasia and I think the probability is very high--one learns not to be too exact--that this decade may bring us the clean dissection of the molecular basis of the cause of at least one form of cancer. And this is going to initiate a long awaited phase of specificity in the prevention and control of this

disease, offering as well a new level of hopefulness to people all over the world.

The fact that so much of the world's research radiates out from here makes the directorship of the National Cancer Institute a position of extraordinary responsibility. We are delighted that today we are here to witness the swearing in of Dr. Vincent T. DeVita as the ninth in a succession of dedicated and gifted people who have led the National Cancer Institute. Vincent, you are the first of the special guests at the dais whom I'd like to introduce today. I speak for all of your colleagues who are delighted at the appointment that you represent. You not only bring a vast amount of energy to the awesome position you have accepted, but you add a great deal of enrichment to an already strong level of upper management at NIH. Vincent, we're delighted to welcome you here today on this occasion in your honor.

I should also like to introduce another important person next to him, Mrs. DeVita--Mary Kay. She's with us because she also symbolizes something very important. Almost all of us here have life mates of one kind or another, and if there's any place where comparison of the amenities between this university and the others comes out so strongly negative it is the special financial sacrifices that the wives and others in the families of our scientists sometimes have to make. Mary Kay, you've already won our hearts over the years with an extraordinary show of courage against unbelievable adversity. I'm delighted that you're here today and wish to assure you how much we want this occasion to be a joyous one for you.

Elizabeth, we welcome you too. I fear you won't see your father any more than you do now. One of the reasons that he's scheduled for "ascension" today is that he's already devoted so much of your time as well as his to the pursuit of one of mankind's most important causes. Thank you for loaning us generously that large portion of his life that is yours, too. At least you greatly enlarge your family today by this act of such unselfishness.

Finally, I must admit that if we are a university, we are one with some extraordinary amenities. We have as the president of this university the President of the United States, and as a Board of Trustees, the Congress. And the activities that go on here are supported, I think willingly and certainly hopefully, by every citizen, every person, in the United States. And that special position among the people allows us also to have as Chancellor the President's own personal representative, the Secretary of the Department of Health and Human Services.

Today is my first opportunity to share this particular podium with Secretary Harris. It does offer me an occasion to issue an emphatic disclaimer to a mischievous canard that arose on a previous occasion here. It was said that I was not on hand for a recent appearance with the Secretary because I preferred to visit another live volcano. Madame Secretary, that is not true. There are some similarities, of course. You're a natural phenomenon. You're extraordinarily active. You have boundless energies. But, in my experience, they are directed most successfully and always to very constructive ends. As your coworkers, we have learned

that as long as we keep moving we don't have to worry about fall-out. Madame Secretary, you have the true admiration of all of us. You've accepted us from the very beginning as part of your domain. You've taken an enormous interest and care in understanding what we are and you've supported us beyond all expectations that we might have of any Secretary. Your presence here adds luster to this occasion. We're simply delighted to have you here this morning to officiate at the swearing in of Vincent DeVita as the next Director of the Cancer Institute. I present Secretary Patricia Roberts Harris.

THE PRACTICE OF CARDIOLOGY IN THE 21ST CENTURY*

by

Donald S. Fredrickson, M.D.**

INTRODUCTION.

I have been a cardiologist-manqué for many years. Were it not so I would not have the conceit to appear in such distinguished company, pretending to predict the future of the practice of cardiology.

In carrying out my part of the bargain, I intend to concentrate on the trends in science as a base for my speculations. Here I am helped by the undeniable parental relationship between research and medical or health practice. Scientific experimentation and observation are the father of the healing arts. The generation time is constantly decreasing through what is called "accelerated technology transfer." I would guess that a decade is a reasonable average lag time. Thus if I try to predict where biomedical research may be in 1990, I should be able to extrapolate to some features of practice in the year 2000. Even so, biomedical and behavioral research--in all the collected health sciences--is moving so fast that a leap to the next decade is along and dangerous jump; and, about to spring, I tremble now on the brink of such a chasm. As the Director of NIH I should know better than anyone the fate of prophets who

* Presented at the Interamerican Congress on Cardiology in San Juan, Puerto Rico, on September 13, 1980.

** Director, National Institutes of Health, Bethesda, Maryland.

prematurely promise new gifts in health to the public patrons of research.

In comparing both scientific understanding and its practical application to health across the various medical subdivisions or specialties, one is impressed by the relative maturity of developments in the cardiovascular area. This is not just a feature of our time. It has existed from the end of the medieval period. The central role and universal distribution of the cardiovascular system led the earliest anatomists to concentrate upon it, as witnessed in Vesalius' texts, for example.

The ceaseless motion of the heart, inspiring a high interest in the intriguing mechanics of the circulation, also made the cardiovascular system a major theme of the earliest physiology and, we may say, of clinical investigation, given the seminal role played by William Harvey in the latter. The cardiovascular system provided subjects for some of the earliest pharmacology, Cannon's development of the concept of homeostasis, and lessons drawn from muscle contractions, like Starling's law. These offer additional evidence of the forward salient represented by cardiovascular science from the post-Galenic to the Modern period.

In our time, the heart has been converted from a secret place, expressly forbidden to surgeons, into a veritable playground for them--one in which they seem to have displaced physicians by having the better cure for nearly every abnormality. If they've yielded hypertension back to the internists, it's mainly because they're now so busy curing angina

through bypass grafts, and arrhythmias by excision. The correction of congenital abnormalities and acquired valvular defects has become so routine that some young physicians may think the heart-lung machine first came to the Americas on the Santa Maria.

The medical achievements in diagnostics which paved the way for the surgeons were no less spectacular in their way. I can remember the day of the first trans-septal left heart catheterization and the first whiffs of labeled krypton. And all of us are aware of the pace in generation of ever-newer, more powerful imaging techniques.

[SLIDE]

I admire now the courageous thrusts of contemporary internists, the resurgence of medical countermeasures to recapture surgical territory taken in the Pectoral Wars . . . the adventuresome bloodless knives which reshape deformed vessels by a force majeure. Or the washing-down with streptokinase at the earliest tinge of pain, purging the premonitory thrombus. Or the reluctant, sometimes nostalgic setting aside of those trusty standbys in "medical management," the beta blockers and nitroglycerine, to make way for new weapons like the calcium antagonists.

Prevention is the true sign of maturation of a medical specialty. Cardiology has been the first to lead successful national crusades to reduce mortality and morbidity from major chronic disease, like hypertension, and ischemic heart disease.

Likewise, cardiology has been a leader in establishing norms for conduct of clinical trials, and for vast epidemiological observations that make possible their better design.

The risk-factor analyses, an important shield in our still primitive attacks upon a disease with multiple causes, will be a hallmark in the history of hygiene in the second half of the 20th century. They have much greater predictive power in populations than in individuals, of course, and they will need augmentation by more specific markers in the years ahead.

After such glittering success, cardiovascular research need not be too anxious because areas within it are now passing through a more static phase. Research has a natural rhythm; systole is followed by diastole, as every cardiologist understands.

In the last few years other areas of research, seeming remote from cardiology, have sprung alive and are now in a phase of luxuriant growth. Intersections of technique and opportunity are passing before us with breathtaking speed. Tomorrow's cardiologist must take note of the showers of luminescence rising above other disciplines. They will be sources of both energy and light for forthcoming penetration of mysteries relevant to cardiovascular science and its practical extensions in the next century. Let me mention just a few of these developments.

Cell Transformation.

It is difficult to exaggerate the magnitude of present-day advances in molecular biology and genetics. The elucidation of.

the genetic code is a dozen years behind us. The mapping of human chromosomes proceeds apace. The magic of recombinant DNA technology has been followed directly by the perfecting of a crucial ability for rapid sequencing of DNA. As each lock on nature's secret is picked, keys for the doors beyond fall into our hands. Surprises exist behind them all. Suddenly there is the startling revelation of long intercalated, non-transcribed segments of DNA within genes of eukaryotes which prokaryotes do not recognize as different. Portions of the guidelines for recombinant DNA research must be revived. Much more importantly, these intercalations represent wide spaces between the evolutionary scale of life that will someday be converted into control of the operation and destiny of certain cells and tissues.

Cell transformation has several meanings. In the narrow sense it means introduction of new genes--pieces of DNA--into the chromosomes. Such alterations occur by action of chemical or physical mutagens, or, in the most intriguing ways, through intervention of helper viruses. The genetic changes may induce in cultured cells another "transformation," changes in the behavior of cells that give them neoplastic properties. Study of these phenomena seems certain to lead us one day soon to the molecular basis of cancer.

The techniques of molecular biology are not so easy to adapt to cardiovascular problems. The theories of cell transformation have not been lost on students of atherosclerosis, however.

Latter day work, particularly in cultured endothelial cells, has illustrated the central role of endothelial smooth muscle cells in generation of the atheroma. Benditt and Benditt in 1973 examined the possibility that smooth muscle cells in fibrous caps--generally accepted as precursors of atheromas--might be growths from single transformed cells. Using patients heterozygous for the x-linked isozymes of glucose-6 phosphate dehydrogenase, they provided evidence that fibrous caps could be "monoclonal." Subsequently, workers in Albany and Johns Hopkins have confirmed these findings of "monotypism" (selection of one of the two types of cells possible in such genetic mosaicism, the normal aorta containing both marker enzymes in a generally random distribution). The workers do not agree, however, that monotypic means monoclonal. Other forces of selection could be operating, and for the present, the mutational origin of vascular lesions remains intriguing speculation.

One of the early uses of mosaicism was the demonstration by Lindner and Garn that leiomyomas of the uterus are monotypic, and likely monoclonal. This leads one, concentrating on cardiovascular prophecies, to wonder about cell transformation in the causation of selective hypertrophy of cardiac muscle

Will the year 2000 bring some evidence of altered somatic cell genes in the genesis of hypertrophic cardiomyopathy? Here, doubtless heterogeneous in origin, is a great collection of disorders, especially important as a cause of sudden death in youth. The echocardiogram, and its descendants, have been of great value in exposing, with non-invasive intelligence, a

tell-tale warp in muscle distribution between septum and ventricular wall in numerous patients, some of whom die suddenly in youth. Could these be "benign tumors of cardiac muscle"? Few tissues are exposed to blood transported mutagens to the same degree as the heart. The presence of familial segregation does not prove genetic cause, but greatly increases the probability of aberrant biochemical control of cellular proliferation.

The subject of hypertrophic cardiomyopathy (HC), or asymmetric septal hypertrophy (ASH) as we learned it at NIH, allows one to make one prediction that seems safe. This is that more names for "HC" or "ASH" will have accumulated by 2001. The list now contains some 60 names used to describe this collection of similar abnormalities since Teare's description in 1958 of "asymmetrical hypertrophy of the heart." The tide has ebbed since a record rate of entry of eight new names in 1966 alone, and we may be in recession.

Clinical nomenclature itself is under great pressure of transformations. More than in some medical specialties today, information transfer about cardiovascular disorders involves a high content of eponymic and anatomical terms. As this field shares the pronounced trend toward higher specificity, and greater use of biochemical and genetic definitions, there will be assurance that the rate of expansion of basic techniques for acquiring new information is also on the increase in cardiology.

The ability to detect and perhaps alter genetic polymorphism will profoundly affect many aspects of medical practice by

2001. Cardiovascular practice in the 21st century will share, at the least, an expanded ability to determine genetic differences between individuals in susceptibility to changing external stresses. The formulas for etiology and the prescriptions for prophylaxis will contain these ever improving coefficients of intrinsic difference. This is good, for medical practice will become more, rather than less, personal in the attention it must give to individuals, and their special differences from the norms.

Immunology.

It is fortunate--almost a necessity--that a "revolution" in the understanding of genetic regulation of cellular metabolism is being accompanied by one in knowledge of the immune system. In cancer, at least, one suspects that it is the constant interplay between somatic cell mutation and immunochemical rejection of aberrant cell-type that protects man, and separates him from birds and some mammals far more susceptible to virus-borne neoplasia. Important immunochemical control of other disease processes now obviously exist as well.

The sweeping revelations of antibody structure, the chemical and stereochemical basis of their specificity, the control of antibody production by a complex set of social interactions between different castes of lymphocytes, and has just begun to explain a number of mysterious conditions. The almost breath-taking arrival of cell "factories," either for production of pure antigens (in prokaryotes bearing recombinant genetic messages) or

great quantities of pure antibodies (in "hybridomas") are but some of the new technologies destined to accomplish a vast increase in understanding and controlling disease. The linkage of the major histocompatibility complex and its Ir genes to the causation of now nearly 40 diseases is of the most extraordinary interest.

How this genetic control of immune responsiveness can be manipulated to affect healing or preservation of health is barely visible now. But the light is steadily moving toward areas long in darkness and much of today's newest laboratory results may be routine stuff in the practice of 21st century medicine.

One effect certainly will be to the introduction of much greater specificity into therapeutic encounters that presently are still of the crudest (non-specific) kind. The nonspecific, blanket suppression now imposed in treatment of autoimmune disorders, in neoplasia, or for the duels between graft and host which render helpless so much of present day attempts at transplantation will yield to highly specific antibodies or cytotoxic T cells and other futuristic weaponry.

The relevance of all this in 2001 to the commonest cardiovascular diseases is not so easy to see. At the least, several important problems will be affected:

1. The vascular manifestations--in kidney, heart, and small vessels everywhere--of the autoimmune diseases should be preventable.

2. The transplantation of kidneys and hearts may once again be accelerated by increasing control of rejection. As encouraging as this sounds, organ-switching is not a primary goal for future healing practice. It is incumbent upon late 20th century medicine to reduce to the minimum the need for such "late-stage" correctives for failures in prevention.
3. Chagas' disease. Investigations of South American trypanosomiasis (Chagas' disease) over the past few years have revealed that *Trypanosoma cruzi* and heart tissues may have cross-reacting antigens. This finding could explain destruction of cardiac muscle cells by killer lymphocytes. In addition, antibodies reacting with cardiac tissues have been obtained from patients with Chagas' disease. It is a late but fervent hope of all of us that the modern science of both North and South Americas can at least eliminate this scourge from our hemisphere. It should be a dedicated effort that we take together.

Receptors and Membranes.

Here is a view of platelets aggregating on the endothelium. First, one thinks of the sticky fingers covered with thromboxane and the great revelations about the prostaglandins. But the sight of platelets reminds us how much better we can visualize and understand the complex world of events going on at all cell surfaces. The concept of receptors has brought rational

understanding of cellular control by circulating agonists and expression of numerous mutations involving some important non-enzymatic gene products. Indeed "receptor-deficiency" looms as one of the commonest qualifiers to be found repeatedly in the taxonomy of diseases in the 21st century.

One thinks quickly of numerous magic sites on cell surfaces that will determine workloads for cardiovascular specialists.

1. Insulin--and Diabetes.
2. Lipoproteins.

Apoproteins--will become the diagnostic indices and perhaps cholesterol and triglyceride measurements can go out with the ultracentrifuges.

Iatrogenic and Other Environmental Cardiovascular Disease.

Economic concerns, if not a more sophisticated curiosity, will drive us in future years to a far better recording of the longitudinal encounters individuals have with occupational or other external hazards and with the medical profession. It is likely that we will see and understand several kinds of "environmental heart disease" where none now exists.

We will certainly recognize more forms of iatrogenic heart disease. This electron-micrograph records the cost of cardiac muscle of the benefits in cancer treatment afforded by adriamycin. I do not predict more destructive medicines in the 21st century because I have already supplied hope for increased specificity of drugs or biologicals. A better recording and

correlation of medicines and medical events, however, will make us far more conscious of the harsh bargains demanded by more powerful and conflicting technologies.

Aging and Cardiovascular Disease.

It is not the primary aim of aging research to reset the biological time clock. Cardiovascular medicine in conjunction with hygienic practices will continue to be the major determinant of life span.

The continuing upward shift in the mean age of populations, however, will have a profound effect on medical practice long before 2001. At least three kinds of heart disease will not grow less common in a continuously aging world:

- 1) Aortic valvular disease--calcification of the (1 $\frac{1}{2}$) with bicuspid aortic valves (more tricuspid calcification, too) while rheumatic and syphilitic disease should continue to decline.
- 2) Electrical failures. (Will there someday be a pacemaker in every 100th? every 10th? person). Adding to the worldwide search for better energy resources.
- 3) Any vascular disease arising from cell transformations will be relatively more important in the aging populations. This conclusion is drawn from analogy with cancer--the cumulative time of exposure to mutagens, the declining DNA repair mechanisms in the cell, and a drop-off in immune competence all are invoked to explain

ascending rates of cancer in older people. And so it may be with vascular tissues.

FINALE.

A recent conversation with a mathematician from Marseilles has given me the insight I needed to conclude this prophesy. He is a student of Zadeh, the Berkeley master of theory and practice with "Fuzzy Sets." This is the theory of the imprecise: mathematical assistance in estimating the "possibility" of membership in a given set, where binary--yes or no--answers do not apply.

Take for example the statements: "minimal cardiac enlargement" or "modest hypercholesterolemia." "Fuzzy set" theory allows one to create equations to determine the fit of an individual determination into the sets of "cardiac enlargement" and "hypercholesterolemia" and, moreover, to fit these into more complex matrices that assist diagnosis, selection of therapy, or estimates of prognosis. With high speed computer assistance, of course, the perceptions, the impressions, the multiple data accessions--hard and soft--are spun into print-out displays of intuition in three or four significant figures.

It is across such new mathematical bridges, spanning the art and the science of medicine, that you and I will walk from the 20th into the 21st century.

Despite what you may hear, the golden age of discovery in the life sciences is now, not yesterday. The greatest promise for accomplishment in medicine is thus tomorrow, not today.

REMARKS*

by

Donald S. Fredrickson, M.D.**

It is fun to be here today. Times are more relaxing than they were some years ago. You asked (in relation to genetic engineering), "Is the role of the Administration to have a gentle hand on the tiller?" I think that is probably true now, but I can tell you that back in 1977 it was both hands on the main sheet and heels dug into the transom.

This town is a stage. I was pleased to be here this morning with Gil Omenn, who is a very gifted member of the Administration, but he illustrates that it is really a repertory company that has most of the boards here. I have to keep up with Gil because I never know whether we will be sitting on the same side of the table. The same thing is true of Paul Rogers, whom I met sitting where you are as he was on the dais--a man who has made an important contribution to biomedical research and who is missed very much indeed. I remember that once we ended up at the F Street Club, which he belongs to and I do not, having a piano duel, two rusty childhood amateurs trying to outdo each other in playing something. I think I came off more brilliantly with the Chopin "Scherzo," a part of which I could remember, but he was

*Presented at the National Conference on "Recombinant DNA and the Federal Government," on October 9, 1980, at the New Marriott Hotel, Bethesda, Maryland.

**Director, National Institutes of Health

learly much more accurate and likely to go a lot further. When he left the Congress I gave him half of "Rachmaninoff's Variations on a Theme by Paganini," and in checking with him the other night we discovered that neither of us has been able to try to learn his part.

There isn't much new I can tell you about the past, of what the NIH Director thought or did about recombinant DNA, because it is deliberately part of a vast public record. If you are ever interested you can come by NIH and pick up your volumes of the DNA papers, half a shelf now of yellow volumes and more to come--every scrap of correspondence, every official meeting, all transcribed; and most of the official thoughts that I had are there. What we will do in the future with regard to specific actions, I cannot talk about either, because we are trying to preserve the careful process, but I can tell you just a little bit of my reminiscences between 1977 and now.

It was three and a half years ago that I went to the platform among many other people at the National Academy of Sciences, with the air acrimonious from the debate on recombinant DNA. Tremendous polarization had taken place: the stage was full of spitballs and torn up posters. And I tried to describe what the government was involved in--in arranging for some kind of orderly procedure that would protect the interests of all; and there were clearly interests that were poles apart, as many of the participants demonstrated.

I remember that later I heard from a friend by the name of Bengt Gustafsson that so violent had been the debate that when I came in to talk a little bit about what the government was doing, he thought that "it was like the Romans coming." Now, I would be flattered by that except for two things. One is that I, being a Swede, know what Swedes mean by their gentle cynicism, and the second is that I certainly felt anything but in command and imperious about the situation at that time. We had finished a public hearing. The guidelines had been issued eight months before. We were in the midst of meetings of the (Federal) Inter-agency Committee on Recombinant DNA research, which still exists. It had been put together as soon as we realized that the guidelines were to be issued after we finally had obtained Presidential blessing for it late in 1976.

That committee, to live up to its mandate, sought to develop consensus among its 25 member agencies, which cover virtually all of the territory of regulation and research for the Federal Government in this field. We sought to understand each other and to respect each agency's interests and anxieties. We looked carefully at legislation, and brought forth some recommendations to the Administration that if it wanted by law to make guidelines applicable to the widespread laboratory use of these techniques, it would indeed have to write a new statute; and we suggested the minimal points that ought to be included in such legislation.

It was shortly after that forum that the action began in the Congress, which Paul Rogers very succinctly described for you. I think he is right that here was a demonstration, and perhaps this

is one of the valuable aspects of the whole affair--that the scientific community, the great middle of it, suddenly awoke and came out to seek the truth, to urge great prudence and deliberation in any attempts to regulate laboratory practices by ironclad regulations. It is difficult to deal with laboratory science--moving as it does--in the mode prescribed by the Federal Administrative Procedure Act, and certainly in any mode prescribed by statute.

The state of affairs today is, of course, very different. There remain some important institutions within government that I should mention further. First of all, the Recombinant DNA Advisory Committee has proved to be a successful experiment in obtaining for the government public advice of an almost binding sort, and in blending those requirements with the extraordinarily important efforts of maintaining creativity throughout the scientific universe. The RAC started out as a group of experts, with one political scientist and then one ethicist. With the revision of the guidelines late in 1978, it was completely converted to what many of us were concerned would be an unsuccessful attempt to compress both technical and policy advice into one group, operating, as it were on, line. I was among those who were concerned, but I did my best to try to convince the then-Secretary, Joe Califano, and the Department staff that this seemed to be a necessary accompaniment to the revision of the guidelines, and I tell you that it has worked thus far.

I believe the success of this mixed body is mainly due to the caliber of its members and to a general change of climate.

We are grateful to Ray Thornton, former Chairman of the Subcommittee on Science, Research and Technology. Having conducted hearings on this subject, he had already demonstrated that a layman can chair a committee dealing with such technical matter and do it with extraordinary flair. When he left the Congress, it was a loss to that body, but some of us were quick to realize, about the time we were to broaden the RAC, that citizens like Ray Thornton could participate effectively in the public governance of science.

The RAC, then, goes on its way. Its recent recommendations are before me for consideration. In its hands, the guidelines have evolved in the direction of removing from coverage certain types of experiments, with the general effect of returning to the institutions the great bulk of the responsibility, leaving only standards to be set by a national body. It is working, and I think we can be generally pleased--I certainly am--with its activities and the direction it has taken so far.

The Interagency Committee does not meet very frequently now; its times of great tempest are over. But it remains an extremely effective organ for communication, so that the agencies which at first had to accept one agency as a lead in this particular activity are reassured: they now view that agency as trying to meet its responsibilities while fully respecting the mandates and responsibilities of the others.

We have had extraordinary cooperation from the research agencies. From the beginning, the National Science Foundation

and the Agriculture Department, among others, were quick to accept the guidelines. They have continued to assist importantly in all the ensuing stages. And I must say, the same is true for all the regulators as well.

The Industrial Practices Subcommittee, which will be of interest to you, has been in place for some months. It is there to deal with the questions that arise when a set of laboratory techniques are converted to more practical applications. It is in place to cope with problems, to advise the parent committee, and to interact with it in the activities that go on.

Much tribute must be paid to the informal RAC-- the kitchen RAC--that we formed way back in the beginning when this matter began to take a third to a half of the time of the Director of NIH, and those are the dedicated staff people and scientists at NIH who made it possible for us to cope with the deluge of problems, the enormous numbers of forces that converged upon this issue. I cannot pay tribute enough to all those individuals. I may say, in a matter of reflection, that it probably would be impossible for an agency coping with scientific matters to have gone as far as we did without the presence on its own campus of a scientific body of extraordinary competence. To have peers of the world's best present is an instrument of a usefulness beyond description maintaining the administrative role of an organization like NIH.

In my view it is not as a Roman that I approach this business today, or really ever did. I much more favor the Greek,

myself--and not the Ionian, because I am not that mathematical or precise. It is much more in the Athenian sense that the real issues that remain--and always were the most important--are the relationship of man to the molecular movement of science; and it is the ethical and moral and human issues that still predominate, and will be the guides to the course of this future activity.

When in 1978 the guidelines were finally revised after an exhausting year, I sent Joe Califano a telegram. I took it to him myself and gave it to his secretary, Muriel Hartley, who was a tough one, and who used to work for Al Haig. I said, "Muriel, this is a telegram from the Vatican," and indeed it was in Latin and I had put a great big red seal on the bottom. To this day, Muriel thinks John Paul II actually did have a hand in its composition. I said, "Habemus regimen recombinatum," among other things. "We have guidelines." If Joe were still there, and Muriel, I would send another telegram in the same poor Latin, something like "Vincemos terrorum"--"We have conquered great fear."

But we are not finished yet with the way to handle gracefully this extraordinary episode, you and I. We must be very prudent in the way we approach the use of this extraordinary power. The ethical issues, after all, will remain--now stronger than the fears of physical containment and infractions. And we need to maintain the universality of science in seeking a common set of principles in which to operate. We have to keep the application of those principles moving to the most practical

locus--which is to the periphery, to local utilization, to the institutions themselves.

One of the aspects of developing guidelines to which we paid a lot of attention from the beginning was the international. NIH was not writing guidelines for the world. We knew that we could not. On the other hand, what the government was doing would clearly have an enormous effect on many other countries. It was obvious that the opportunity to realize the full value of these techniques would depend a lot on national views of regulation. Whole equilibria might shift if different views were taken in this issue.

I suppose I visited half the world, not for this purpose alone but trying whenever I was in a country to stop in to talk to the local guideline authorities. The differences between Japan, GMAG in Great Britain, and the Soviet Union are very interesting. Basically, though, we are in equilibrium, and I don't think there is any discrepancy of great significance around the world. I know that some of you and your companies here are very much au courant with that. I don't blame you for testing the waters on both sides. I think that we will, however, have a relatively common set of world standards provided we keep the process of evolution going. If GMAG today is down a little lower and the Brenner formulas have changed their numbers, the recommendations of the RAC seem to be pointing the same way. So this important aspect of competition in world markets and exploitation is something we have not forgotten from the beginning and will, so long as we have guidelines, be concerned with.

As you know, when we first promulgated the guidelines, we asked industry first. Somebody from one of the companies said that this was the first time in his experience the government had asked anybody in to discuss what it might do--to get your opinions. I think that was appropriate, and we have tried to continue it, consulting those who want to use this technique for profit, along with all the extremes of opinion--which range across the board--for the concerns we all have, profitmakers or not, for public safety.

I suppose I am concerned about only one thing, and it's not something we can do a great deal about. I realize that some of the universality of science is always threatened when there is an enormous competition for exploitation of creative ideas. And I hope we do not see a breakdown in communication among scientists --that we do not make the whole world proprietary. This may be the view of a romantic. People say, "Well, look at the chemists; they did that 30 years ago." I look at the chemists and I am not always so happy about the course of chemistry since it became an extremely important industrial property.

I think it is inevitable and necessary that these inventions be used practically, and it is important that people make profit from them because that's the way they will move the farthest and fastest. But still, all of you who are concerned about this aspect need to pay careful attention. I think we are going to remain in a voluntary mode, and we will do so as long as we retain our grace and our etiquette in carrying out its responsibilities. There will be ethical issues. And here I am no more

concerned about the industrial sector than I am about the university--all of us caught up in a competitive world. We need to be careful, though, because something is involved here that is related to the future of generations yet to come, to a sector of science that is much bigger than microbiology or genetics: the proof that science can continue to play a responsible role when its powers have become so awesome.

Question: NIH has persistently denied that it wanted to be, and has attempted not to be, a regulator in relation to recombinant DNA. What is your attitude toward the role that NIH would continue to play as more and more regulatory agencies perhaps find activities now within their mandates?

Answer: First of all, I am of the strong belief that there should be only one national body wherein we attempt to synthesize movements of knowledge in science into some kind of pattern for standards. Any attempt to have more than one body doing this kind of synthesis would be a very serious move back toward the fragmentation that threatened some years ago. I think that NIH--which basically was a center for evolution of the guidelines--will continue to offer to house and to service that kind of body as long as these standards need to be set. And I would guess that we will be able to interrelate these activities to the regulatory agencies for some time.

The big pressure is going to be on the question of handling larger and larger volumes of proprietary information. At first

we said we thought it couldn't be done, or it shouldn't be done at NIH. We decided to do it. I think it has worked. The agencies that might have regulatory interest, as you know, are there on the RAC as ex-officio members. They keep themselves informed, as I think they must. I do not know what the future will bring because I do not think any of us can foresee exactly what kind of problems are going to be created and what will be the role of the agencies for regulation. NIH will try to continue in that role as long as it can, at least in terms of providing a center for reference. It will house as objective and competent a scientific group of information givers and synthesizers as could possibly be assembled in this country.

This matter of regulation is something we will all have to work out together. Clearly, the regulatory agencies are going to see their authorities and mandates moving inevitably toward the control of certain products. That is why we keep the Interagency Committee there. The machinery is oiled; we can meet very quickly and deal--appropriately, I hope--with problems as they arise. The mechanisms are there to be used when necessary.

IS THERE A FEDERAL PHILOSOPHY ABOUT ACADEMIC MEDICINE?*

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FEDERAL INTERVENTION IN HIGHER EDUCATION

"Two great impacts, beyond all other forces, have molded the modern American university system and made it distinctive.... Both have come primarily from the Federal government. Both have come in response to national needs." So wrote Clark Kerr in 1964.¹ The two impacts he selected were the Morrill Land Grant Act of 1862 and the commencement of federal support of scientific research beginning in World War II.

The biomedical research arising from the second commitment came to be supported and conducted largely through the National Institutes of Health, for many years now the largest single source of funds for research and development in American universities. At its inception this was the first and only federal intervention in academic medicine, and for over 30 years it remained the preeminent one.

Today the field has diversified (Table I). The sum of departments, their subsidiaries, and other independent agencies with mandates and budgets affecting the academic medical centers constitutes a veritable Tower of Babel (Figure 1). Actually, the number of agencies should perhaps be multiplied by three or four to take account of the interested congressional committees. And that product should be increased by one or two more to avoid slighting such influential overseers as the Office of Management and Budget and the General Accounting Office.

Has the federal philosophy on academic medicine changed with the mushrooming growth of interests? Is there a federal philosophy on this subject? Was there ever one?

The federal commitments to harness the universities for the enhance-

*Presented as part of a *Symposium on the Academic Physician: An Endangered Species* held by the Committee on Medical Education of the New York Academy of Medicine October 10, 1980.

TABLE I. FEDERAL AGENCIES HAVING PROGRAMS OR AUTHORITY INVOLVING ACADEMIC MEDICAL CENTERS

<i>Departments</i>
Agriculture
Defense
Energy
Labor
Health and Human Services
Office of Civil Rights
Office of Inspector General
Office of Human Development Services
Health Care Financing Administration
National Center for Health Care Technology
National Center for Health Services Research
Alcohol, Drug Abuse, and Mental Health Administration
Center for Disease Control
Food and Drug Administration
Health Resources Administration
Health Services Administration
National Institutes of Health
<i>Independent agencies</i>
Environmental Protection Agency
Equal Employment Opportunity Commission
National Aeronautics and Space Administration
National Science Foundation
Nuclear Regulatory Commission
Small Business Administration
Veterans Administration

ment of agriculture and the natural sciences expressed broad popular intent to have American universities achieve objectives both utilitarian and egalitarian. Today that philosophical core remains as strong and influential as ever.

FOUNDATIONS BEFORE FEDERALISM

The marriage of science and medicine in America was a private affair. The brokers were philanthropists and private foundations, who then played a dominant role in shaping medical education at the turn of the 20th century. The federal government would not be involved significantly before World War II.

The renaissance in medical education following publication of the Flexner Report in 1910 took place entirely without federal intervention.² The major agents of change were the American Medical Association (AMA), the Association of American Medical Colleges (AAMC), and

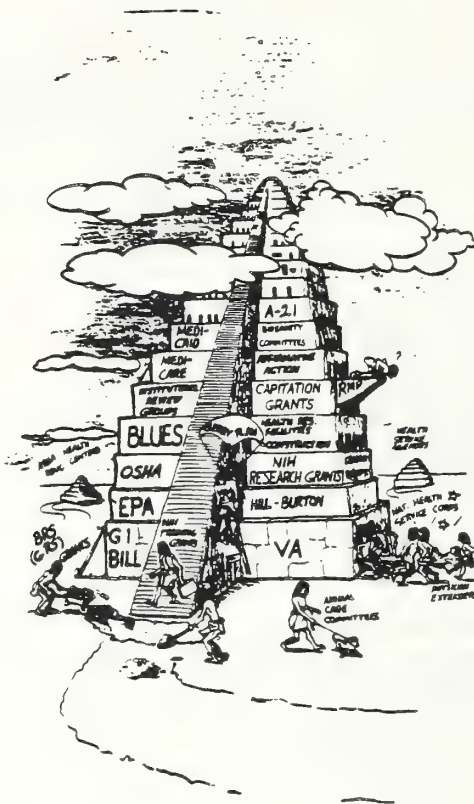


Fig. 1. Ziggurat of the Babylonian type suggesting a modern medical center with its accretion of participating federal programs

the state governments, which legislated accreditation requirements that many proprietary schools could not meet. One can imagine the uproar if the Congress had demanded acceptance of Flexner's recommendations and thus caused the deaths of 76 medical schools, with a generous share of the fatalities during the administration of William Howard Taft!

Flexner's investigation was underwritten by the Carnegie Foundation for the Advancement of Teaching. He left Carnegie about 1911 to become a member of the staff of the Rockefeller General Education Board. There he used the leverage of Rockefeller philanthropy to promote full-time clinical professorships. The first such grant was to Johns Hopkins in 1913, and was an idea radical enough to be opposed by the AMA, its Council on Medical Education, President Eliot of Harvard, and many others.

An analysis of the major foundations and their important influences exceeds my present intent. To the extent that philanthropy still contributes to the support of biomedical research, it provides an essential relief from some constraints inevitable in public funding. To the extent that foundations now lend most of their resources to encourage the medical centers to better their service and teaching functions, they have helped to balance the support of academic medicine. Some foundations have also sought to bring about further metamorphoses in the self-identity of the institutions. But these changes, where perceived as imposing too great a burden of service and community obligation, contribute to the concerns of clinical investigators and other academic physicians that they may be an endangered species.

EARLY MEDICAL FEDERALISM

During the 1930s the federal government, through the New Deal, became more active in matters of health. Its interventions, however, were principally confined to "public health," with little involvement in academic medicine per se. In fiscal 1941 only six of the 71 four-year medical schools reported any income at all from the government.

The end of the decade, however, saw the first awakening of the government's interest in extending its partnership with academia beyond agricultural arts and sciences. The Ransdell Act of 1930, which created the National Institutes of Health (NIH), and the National Cancer Act of 1937 provided funds not only for intramural research but for grants and fellowships to institutions outside the Public Health Service.

During World War II the Armed Forces sustained the medical schools in part through the Army Specialized Training Program (ASTP) and the Navy V-12 Program for medical students. The G.I. Bill for veterans made it possible for many of the present senior leaders in academic medicine to enter the profession.

In January 1946 the Veterans Administration authorized affiliation of its hospitals with schools of medicine. This invaluable partnership continues today, salvaged periodically by salary adjustments for Veterans Administration employees which allow the hospitals to remain in competition for qualified staff.

IMMEDIATELY AFTER WORLD WAR II

In 1946 The National Institutes of Health took over the research grants being made by the wartime Office of Scientific Research and Develop-

ment. The rapid growth of the Institutes and the interdependence that quickly developed between the agency and academic medical centers were soon to change radically the recipient institutions.

In 1948 the National Cancer Institute was joined by separate Institutes for Mental Health, Heart, and Dental Research, continuing the categorical approach of federal funding for biomedical science that has prevailed to the present time. Another important aspect of this intervention has been the far greater role assumed by the legislative than the executive branch in determining the growth and character of National Institutes of Health funding.

In fiscal 1948 the NIH budget was \$29 million. By then all but two of the 71 four-year medical schools were receiving federal (NIH) grants. Amounts varied widely from school to school. The smallest was \$4,000 and the largest \$1.5 million.

Then as now, the principal instrument used for support was the research project grant to individual scientists. It had become a key philosophical tenet that awards should be based primarily on peer judgment of scientific excellence. During the intervening years this requirement has been repeatedly upheld and even written into the statutory authorities of the Institutes. Last year the president specified in his budget and the Congress affirmed that investigator-initiated research project grants had the first priority in continuing federal support of health science.

THREATENED IMBALANCE

It was not long after the beginning of NIH grants that concern arose about undesirable effects of supporting a single academic function through awards to individual scientists. An early decision by the National Advisory Health Council, the original group charged with recommending grants, had prohibited payment of indirect costs. At the insistence of grantee institutions, this position was soon reversed and up to 8% of the total was reimbursed. Gradually the amount permitted has increased to its current mean of nearly 30%.

In 1950 an AMA-AAMC Survey of Medical Education supported by the Kellogg Foundation concluded that the need for academic medicine "is for institutional—not project—support."³ Joseph S. Murtaugh of NIH wrote in 1972: "It was apparent in the late 1950s that broad use of the project system... introduced a substantial element of instability into the academic structure."⁴ The Bayne Jones Report of 1958 advocated a "base

grant," or general research support grant, designed to strengthen and to stabilize research studies by complementing more directed forms of biomedical research support.⁵ Although the original authorization passed by the Congress for general research support funds (P.L. 86-798, 1960) permitted the Institutes to allocate as much as 15% of their research budgets to such grants, the highest amount awarded was 8%. Currently, the successor Biomedical Research Support Grants program amounts to about 1.5% of the research budget. The steep decline in this form of institutional support is a philosophical issue inside the administration and certain committees in the Congress. It is also a practical matter of considerable importance to the institutions. A new balance needs to be struck during the 1980s.

Looking back, one marvels at the flowering of the marriage between science and medicine stimulated by NIH support. As the science base for medicine expanded, more faculty members became interested in research and more needed to be trained to translate the new discoveries into health practices. New waves of technology arising from chemistry, nuclear physics, and other basic disciplines underwent similar expansion through federal support to universities from the Atomic Energy Commission (established in 1946), the National Science Foundation (1950), and other agencies, adding to the upward spiraling opportunities for new knowledge. There were also complaints, some reaching a crescendo in the last decade, that the attention of the academic medical centers was distracted too far in the direction of science and technology.

Imbalances did occur. There was a shortage of time devoted to teaching. The space given to instruction dwindled as more laboratory space was required. Some of the distortion could have been corrected but for a generally accepted taboo against federal support of education per se prior to the 1960s. Not only organized medicine but many other factions in the American society were opposed to it.

Attempts were made in the late 1950s to pass legislation for construction of facilities for medical teaching as well as for research. Only by striking the former was it possible to pass the Health Research Construction Act of 1956. Indeed, the Congress, apparently urged by the AMA, held to a narrow view of federal intervention in academic medicine. Congressman John Fogarty's powerful voice on the House Appropriations Committee warned the NIH in 1957 that funds for medical research were not to be spent for broad support of medical education.

New temptations to comingle support for research and teaching arose as research training became more necessary and more popular. The addition of new Institutes to the NIH and the increasing budget promised that research could become a full-time career. And, as knowledge rapidly expanded, the need for professional scientists to replace part-time amateurs grew apace.

One by one, the new categorical Institutes were created, each with authorizing legislation calling for the establishment of fellowships for research. The authorities also called for training related to diagnosis and treatment. Soon training grants exceeded fellowships as vehicles to meet training responsibilities.

TRAINING GRANTS

The multipurpose training grants were probably the most important federal influence on academic medicine for about 20 years. They became an effective instrument to help schools to develop in every department. Indeed, powerful forces for change sometimes intruded heavily on internal academic matters. Some disciplines lacked strong academic or research traditions. It was not official policy, but study sections and site visitors are said to have advised, pointedly, that training grants in some disciplines were much more likely to go to separate divisions or departments than to mere sections of the parent medicine or surgery department. Thus, the growth of subspecialization arising from new technology brought unavoidable changes in both the curriculum and the organization of the medical schools.

WHITHER TRAINING SUPPORT?

NIH support for training in biomedical research has declined from \$168 million to \$148 million over the last 10 years (1969-1979). Several factors have contributed. In the early 1960s a policy decision of NIH Director James A. Shannon narrowed the mix of clinical and research training under NIH training grants toward research alone. In 1974 a payback clause was introduced in the act authorizing National Research Service Awards (P.L. 93-348). Perhaps coincidentally, a steep decline began in M.D. applicants for training, and continued until the proportion of postdoctoral trainees having M.D. degrees has now fallen considerably below those with Ph.D. degrees.

The tightening of the federal budget in the late 1960s brought the

prospect of a plateau in research grant support. President Richard Nixon's attempted impoundment of the Congress's budget increases for the NIH, as well as delays in reauthorization of the National Research Act, contributed to an on-again, off-again period of confusion about research training. An annual study of the needs for training by the National Academy of Sciences, mandated by the Act, continues. Federal support for research training is a crucial philosophical issue needing resolution in the 1980s. The problem of the missing clinical investigator is complex. There is no single solution, but a much needed ingredient is a clarification of government intent.

One important carryover of the egalitarian spirit of the earliest Federal intervention affecting the medical centers is the development of strong NIH programs designed to increase the proportion of ethnic minorities and women entering the mainstream of health research. These efforts must be sustained even if overall funding should decline.

CONSTRUCTION OF CLINICAL FACILITIES

The Hospital Survey and Construction Act of 1946 (Hill-Burton) was a source of funds for modernization or construction of clinical facilities needed by practically all medical schools. By 1965 the federal government had provided almost \$2 billion to match \$4 billion to construct 6,700 projects involving 285,000 beds. During the next 10 years the Congress appropriated another \$2 billion. After 1970 the emphasis shifted to modernization of existing hospitals and construction of outpatient facilities.

FEDERAL SUPPORT OF MEDICAL CARE

Enactment of Medicare and Medicaid in the mid-1960s had an extraordinary effect on academic medical centers. This new source of income has done for service and clinical teaching what NIH funds have done for research.

When third-party coverage was extended to former "charity" patients, the latter gained the freedom to choose providers. Teaching clinics that had been operated with insufficient regard for the convenience of their patients found themselves without subjects. The grim features of former charity wards were at last dispelled by renovations, inspired by compulsory federal standards and by a simpler rule of the marketplace: patients could now elect to go elsewhere.

TABLE II. IMPACT OF SERVICE INCOME AND R&D ON MEDICAL SCHOOL REVENUES, 1960-1978

	<i>Millions of dollars</i>					<i>Percent</i>				
	1960	1965	1970	1975	1978	1960	1965	1970	1975	1978
Total revenue*	\$436	\$882	\$1,713	\$3,389	\$4,906	100%	100%	100%	100%	100%
Service income**	n.a.	55	179	655†	1,082	n.a.	6	10	19	22
Total R&D†	187	434	582	1,050	1,368	43	49	34	31	28
(federal R&D)†	(136)	(361)	(455)	(864)	(1,127)	(31)	(41)	(27)	(25)	(23)
Other	n.a.	393	952	1,684	2,456	n.a.	45	56	50	50

*Excludes capital funding and hospital costs recovered from patients and third parties.

**Includes physicians' fees from patients and third parties. Excludes revenues from sponsored service programs.

†Represents sponsored R&D (research grants and contracts). Includes indirect costs recovered for R&D and other sponsored programs.

‡Estimated.

Source: Association of American Medical Colleges

Also important was the acquisition of professional fees as a source of support for physicians, house staff, and other academic affairs (Table II). Another rapidly expanding source of revenues has been state and local government funding. Thus, federal funds for research in medical schools, although continuing to rise, have declined considerably over the last 10 or 15 years as a proportion of the schools' total revenues for educational purposes. Federal research support as a proportion of total research in medical schools has not changed appreciably during that same period.

REGIONAL MEDICAL PROGRAMS

In the mid-1960s Lyndon Johnson, at the urging of a group of prominent academicians and other friends of academic medicine, swung his support to convince the Congress to enact legislation for Regional Medical Programs designed to induce medical schools to increase their community involvement. By offering federal support for staffing and projects approved by the Department of Health, Education, and Welfare,* Regional Medical Programs emphasized continuing education for health professionals, with the medical school as the hub of a regional program.

It is noteworthy that at first the Congress entrusted the NIH with

*Split into a Department of Education and a Department of Health and Human Services on May 7, 1980.

fostering these programs. The departure from scientific orthodoxy, however, was too much for the Institutes, and the Regional Medical Programs, by the time of their lingering death in the early 1970s, were housed in another conglomerate agency. Many patterns of interinstitutional collaboration brought into being through Regional Medical Programs have persisted and expanded.

STUDENT LOANS AND CAPITATIONS

A growing concern over an impending shortage of physicians generated pressures that led to enactment in 1963 of the Health Professions Assistance Act. Here, at last, was direct federal support for medical education through construction and student loans. The authority of this legislation was broadened in 1965 and 1966, and more comprehensive means of federal support to developmental and basic improvement grants were provided by the Health Manpower Act of 1968. Capitation supports were offered to increase enrollments. In the Department of Health, Education and Welfare reorganization of 1968, the Bureau of Manpower Education, was placed in the NIH, on grounds that the NIH was the agency in closest contact with academic medicine. But, again, the marriage did not last, and the bureau was transferred from the NIH in 1973 to form the core of the new Health Resources Administration.

Under the impetus of this federal funding, there was an unprecedented expansion of facilities for training professional health personnel. In the decade ending in 1976 a total of 41 new health professional schools—including 28 schools of medicine and osteopathy—were opened. The annual number of medical and osteopathic graduates rose by 85%.

In the late 1960s and early 1970s an effort to meet the long-felt need for better balance between research and training took the form of direct support to the schools, but was tied to the movement to increase the number of physicians entering family practice (P.L. 91-696 and P.L. 92-157, Sec. 107). Figure 2 depicts one of the heroic efforts exerted by the Congress to save American medicine from elitism and overspecialization.

Today we have more than 450,000 physicians—nearly double the number in the early 1960s—and the schools are turning out about 15,000 new physicians each year. The Graduate Medical Education National Advisory Committee, a body of academic and other experts, predicts that by 1990 we may reach a level of 536,000 licensed practicing physicians in this country. The Committee has recently announced conclusions that this



Fig. 2. The edifice of medical education as once perceived by some members of the Congress (c. 1970), who sought to preserve equilibrium by heroic efforts

would constitute a gross surplus of about 70,000, with substantial *shortages* in some specialties and continued unevenness in geographic distribution.⁶ Obviously, the implications of these findings must be examined carefully. Figure 3 is a fanciful projection of the consequences to be expected from precipitous reaction to such dire predictions.

By 1976 federal support for health professional education began to de-emphasize expansion of training capacity and to concentrate on the maldistribution problem—both as to areas of specialization and to geographic availability of physicians. The moves reinforced utilitarian impulse rather than serious turns in ideology. Federal carrots were offered to develop training programs for family practice. The National Health Service Corps was set up, offering rewards to the would-be health professional personnel who participated in the program. The Corps was designed to improve the distribution and retention of physicians and other health care personnel in chronically underserved areas.



Fig. 3. The structure of academic medicine has recently been appraised from two positions. The Graduate Medical Education National Advisory Committee has suggested a reduction in size to avoid a gross surplus of physicians by 1990;⁶ and Milton Friedman, the Nobel-winning economist, would knock the tax supports out of the foundation (see *Science*, October 3, 1980, p. 33).

The Area Health Education Center program, like the Regional Medical Programs, rewarded institutions for reaching outside their walls, linking their academic resources and training programs to community hospitals and other local institutions to address the communities' training needs for health professions. The program, now involving 37 medical schools, emphasizes primary care and provides support for graduate and undergraduate training programs in medicine, nursing, dentistry, pharmacy, and the allied health professions.

Preliminary findings show that the program seems to be achieving its goal of improving the distribution of health care providers and inducing medical students in greater numbers to enter primary care residencies.

RIISING PHILOSOPHICAL CONFLICTS

Different bills are now before the Congress that reflect some of the sharpest differences in philosophy on medical education and biomedical research since the beginning of federal intervention. Reauthorization of the Health Manpower Act involves a test between those who want to eliminate or drastically to reduce capitation support and those who favor its continuation, with or without attached conditions, that have helped determine class size and added many hours of family medicine or primary care to the curriculum.

At the same time, radical changes in the authorization of the NIH are being considered by the Congress. A House bill would replace Section 301 of the Public Health Service Act—the source of continuity for NIH research programs for many years—with the orthodox cycle of reauthorizations setting time and dollar limits on the actions of the appropriation committees. A Senate bill removes such restrictions now applying to cancer, heart, and training programs, but adds a President's Council to recommend annual budgets for support of all health science.

A mixture of philosophical and more mundane conflicts is involved. Academic medicine has shaken off any reluctance to enter the debate, and from published news reports has favored the Senate approach of maximizing public input into preparation of the president's budget for research while protecting the hallowed statutory lifeline assuring continuity of the NIH.⁷

REGULATION

Federal support is everywhere accompanied by some tax in procedure. This is partly reckoned in requirements to show fiscal accountability. Other exercises in morality are also charged—demands that change within the ethical frames of reference obtaining in this country and in the world at large. Not a little of the rise in procedural tax is due to astonishing increases in the power of biological research to extend lives and affect living things. A complex structure of regulation and administrative law continues to arise from heightened public awareness, and sometimes anxiety, about the potential for harm as well as good in the new technologies.

There is a prevailing federal policy on some of the regulation that accompanies the supply of public funds for both animal and human experimentation. This is an emphasis upon the setting of uniform national or even international standards for humane and safe practices and the enforcing of the standards locally in the institutions. The NIH guidelines

for recombinant DNA research have provided a recent valuable experiment in applying special precautions. Local determination under national guidelines is rapidly being restored, and institutions have demonstrated an admirable capability to accept the burden of self-regulation. This victory of sensible regulation is one that the NIH and the academic communities have won by working together with the public, and all of us share a deep interest in holding to this principle.

The situation in respect to requisites for demonstration of fiscal accountability is presently far less admirable. Few universities have accounting systems equal to the time-and-effort requirements imposed upon grantees and contractors by federal auditors. There has been a lamentable failure of the research program managers and the audit or fiscal authorities in the federal government to work together in constructing feasible systems to keep accounts and to detect fraud appropriate to the nature of scientific investigation and its necessary admixture of teaching and medical practice.

There is just cause for academic anxiety about such fiscal accounting requirements as are exacted by Office of Management and Budget Circular A-21; about how civil rights legislation will be implemented, including the subcontracting strictures of the Acts (like P.L. 95-907) designed to increase access to government contracts with small businesses run by minorities and women; about some of the conflicting agency views concerning the duties of institutional review boards; and about the attempts of some state or regional Health Planning Agencies to determine the appropriateness of equipment or facilities awarded for research in teaching hospitals.

The major federal agencies involved with the academic medical centers—especially the National Institutes of Health and the parent Public Health Service—have a definite responsibility to foster ecumenical resolution of conflicts in procedures between diverse government agencies. They must also speak clearly to both the Congress and the executive branch about how academic institutions are best enabled to serve the public needs. At the same time one also cannot overemphasize the need for universities to foster consensus in and among themselves about the best avenues to sensible compromise and accommodation to reasonable public demands. Sometimes the university community least understands the tensions created by division of faculty loyalties between alma mater and financial patron.

ORACULAR EXERCISE

That last thought should set the azimuth for a glimpse into the horizon. Despite their sense of thralldom, American academic medical centers are always potentially in command of their own destinies. If they deplore having become public utilities, they at least are most assuredly essential ones. And as such they have enormous strength when deployed in a unified and reasonable position.

The pluralism of federal influences upon academic medicine also has virtues that soften any uneven contours in federal philosophies. A monolithic agency funding all the academic recipients from a single budget could be disastrous. The total support derived would almost certainly be less than it is now. At the opposite end, we are also fortunate to have been spared the paralyzing partition of government interests between too many powerful, separate, and contending ministries of health, science, education, culture, etc. This kind of dispersion in some other countries has made more difficult the harnessing of academic science to problems of public health.

As for research, the contribution of federal funds to support it in academic health centers is likely to remain at its present 70 to 80%. A continuation of the funding of research from private and nonfederal government sources remains as important as ever. Current attempts to attract businesses to provide support in greater amounts is highly commendable. One hopes, of course, that constraints on academic freedom attached to corporate funding would be less than those attached to the public purse, but this seems doubtful.

It is alarming to hear sanguine expressions of confidence that private patrons would come forth to support all worthwhile scientific research if the government withdrew. One is reminded of the dismal failure of the National Research Fund, established in 1926 to channel industrial funds into basic research. A goal of \$20 million over a 10-year period was set, but only \$379,660 was received by 1930. Four years later \$356,402 was returned to the contributors.⁸

The proportion of total medical center revenues that flow from the NIH and other federal research sources is well below what it was 15 years ago (Table II), and the ability of these funds to reshape or change drastically the roles of the medical schools has passed its peak. The basic accommodation has been made, and the search today is for stabilization of the system for inquiry created in the schools through two decades of rapid growth and a recent leveling off.

A curious thing about the leveling off of growth in the scientific effort is the strain it places on the present mechanism to maintain productivity. The health applications of the basic inventions arising from earlier efforts in chemistry and biology have increased dramatically in the last decade. The areas of genetics and immunology are two striking cases in point. Adaptation to asymmetrical opportunities and the provision of trained specialists to take practical advantage of them cannot be met in the same manner as before. The past answer was general growth. If economic constraints on the size of the total system cannot be relieved, then there must be displacement of resources from one field to another—shifts that relate to both research and training.

Redeployment of effort in a "zero-sum game" requires philosophic delicacy that does not come easily to organizations adapted splendidly to general expansion. Arrangements have to be made to protect areas in diastole (a necessary part of the rhythm in research and development) and to maintain the proper balance between fundamental inquiry and practical application. And priorities must be established without departure from the scientific quality requisite for any biomedical support. So far as biomedical research is concerned, the highly categorical NIH, the executive layers above and around them, the Congress, and the academic medical centers—all of them—must examine the future together. Each will need to make some adaptations to sustain the original intentions.

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NOTES FOR OPENING REMARKS
at
THE MEETING OF
CHAIRPERSONS OF INSTITUTIONAL BIOSAFETY COMMITTEES
The Shoreham Hotel, Washington, D.C.
Monday, November 24, 1980

The original NIH Guidelines for Recombinant DNA Research were issued in June 1976. There was a 2 and a half year period between issuance of the original Guidelines and their first revision in December 1978. Just prior to that revision, in November 1978, we called a meeting of IBC Chairmen to discuss the pending revisions. Now, two years later, we have called this second meeting of IBC Chairmen.

Since December 1978, we have revised the Guidelines essentially every three months, following each meeting of the NIH Recombinant DNA Advisory Committee (RAC). We published a complete revised version of the Guidelines in January 1980, and now again just this month, November 1980.

I am pleased that Ray Thornton assumed the Chairmanship of the RAC in July of this year. I am pleased that Dick Krause and the National Institute of Allergy and Infectious Diseases have assumed increasing responsibilities in regard to the Guidelines, including the organization of this meeting. Later this morning, you will be hearing from: Dick Krause on the objectives of this conference; Bill Gartland on the revisions of the Guidelines; and Ray Thornton on the operation of the RAC. The simultaneous workshop sessions this afternoon will allow intensive discussion of many issues of great importance to you and to

the NIH. Tomorrow afternoon's session, moderated by Emmett Barkley, will deal with issues other than recombinant DNA which impact on biomedical science -- classification of etiologic agents, chemical carcinogens, disposal of toxic wastes.

The latest revision of the Guidelines promulgated this month greatly decreases the amount of paper that will have to flow from your IBCs to NIH. The question has been raised as to whether it would be useful for IBCs to send an annual report to NIH on the recombinant DNA research being done at their institutions. I look forward to your expressing your views on this issue, as on many other issues before you, during this meeting.

I am pleased that this meeting includes not only chairmen of IBCs where NIH is funding recombinant DNA research, but also the Chairmen of industrial IBCs, where there is voluntary compliance with the Guidelines. I believe the Voluntary Compliance Program is working well.

Lastly, I want to express my deep appreciation and thanks to you for performing yeoman's service on your IBCs. This task is often thankless. It involves taking time from your own research and other duties. But it is vitally important to science and to society.

NIH DIRECTOR'S AWARD RECIPIENTS CEREMONY
MASUR AUDITORIUM, CLINICAL CENTER
NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND
MONDAY 1 DECEMBER

HER DYNAMIC LEADERSHIP, INITIATIVE, AND PROFESSIONALISM WERE CRITICAL TO THE SUCCESSFUL LAUNCHING OF THE SOCIAL AND BEHAVIORAL SCIENCE PROGRAMS OF THE NATIONAL INSTITUTE ON AGING.

SHE IS A HEALTH SCIENTIST ADMINISTRATOR, SOCIAL AND BEHAVIORAL SCIENCES PROGRAM, IN THE AGING INSTITUTE.

SHIRLEY BAGLEY

FOR 27 YEARS HE HAS PROVIDED CHEERFUL ASSISTANCE AND OUTSTANDING SERVICE TO PATIENTS, VISITORS, AND STAFF IN THE CLINICAL CENTER.

HE IS AN ELEVATOR OPERATOR IN THE CLINICAL CENTER.

JOHN H. BOTTS

FOR CHARTING THE COMPLEXITIES OF THE NIH GRANTS PROGRAMS WITH INGENUITY AND PERSISTENCE, HIS EFFORTS HAVE ENABLED THE NIH TO MAINTAIN A STEADY COURSE IN UNCERTAIN TIMES.

HE IS CHIEF, REPORTS, ANALYSIS AND PRESENTATION SECTION, DIVISION OF RESEARCH GRANTS.

JOSEPH A. BRACKETT

HER EXTRAORDINARY SKILL IN MANAGING THE PEER REVIEW OF SENSITIVE AND COMPLEX GRANT REQUESTS HAS SERVED THE IMPERATIVE OF SCIENTIFIC INTEGRITY.

SHE IS ASSISTANT CHIEF FOR SPECIAL REVIEW, DIVISION OF RESEARCH GRANTS.

BARBARA S. BYNUM

THIS INDIVIDUAL IS THE DIRECTOR'S 'AMBASSADOR OF GOOD WILL' IN THE SERVICE OF ALL NIH.

HE IS A MOTOR VEHICLE OPERATOR, OFFICE OF ADMINISTRATION, OFFICE OF THE DIRECTOR.

JAMES V. CARTER

HER CREATIVITY, SENSITIVITY, AND PERSERVERANCE HAS PROVIDED LEADERSHIP IN THE DEVELOPMENT OF HYPERTENSION EDUCATION AND CONTROL EFFORTS FOR MINORITIES AND THE DISADVANTAGED.

SHE IS PUBLIC HEALTH EDUCATOR, OFFICE OF PREVENTION, EDUCATION AND CONTROL, HEALTH EDUCATION BRANCH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.

ANNIE R. COLLINS

HIS CONCERN FOR ELECTRICAL SAFETY HAS PROTECTED NIH PATIENTS AND HIS COMPETENCE AS AN ELECTRONICS DESIGN ENGINEER IS INTERNATIONALLY RECOGNIZED.

HE IS AN ELECTRONICS ENGINEER, BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH, DIVISION OF RESEARCH SERVICES.

ROLAND CORSEY

HIS CREATIVE CONTRIBUTIONS TO ADMINISTRATIVE MANAGEMENT HAS SUPPORTED NIH GENERALLY, AND THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES IN PARTICULAR.

HE IS NIEHS ASSISTANT EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES.

ROBERT P. CULLEN

IT IS SAID THAT HE BRINGS US LIGHT AND ENERGY WITH DEDICATION AND SUPERIOR TECHNICAL SKILL.

HE IS AN ELECTRICIAN, DIVISION OF ENGINEERING SERVICES, OFFICE OF THE DIRECTOR.

FRANCIS T. DEKORTE

THIS PERSON IS THE FATHER OF WYLBUR—THAT UBIQUITOUS, CONSTANT, AND EFFICIENT SERVANT THAT BENEFITS RESEARCHERS AND MANAGERS IN NIH LABORATORIES AND OFFICES.

HE IS COMPUTER SPECIALIST, COMPUTER CENTER BRANCH, DIVISION OF
COMPUTER RESEARCH AND TECHNOLOGY.

ROGER FAJMAN

HIS DEVELOPMENT OF "MOLECULAR GRAPHICS" HAS MADE IT POSSIBLE TO SEE THE UNSEEN AND TO STUDY THE THREE-DIMENSIONAL STRUCTURE OF BIOLOGICALLY IMPORTANT PROTEIN MOLECULES.

HE IS COMPUTER SPECIALIST, COMPUTER CENTER BRANCH, DIVISION OF
COMPUTER RESEARCH AND TECHNOLOGY.

RICHARD J. FELDMANN

HE HAS PROVIDED DEDICATED SERVICE TO PATIENTS IN NIH CARE AND HAS TAUGHT HIS YOUNG CO-WORKERS IMPORTANT LESSONS IN LIVING BY HIS PERSONAL EXAMPLE.

HE IS SUPERVISORY ADMINISTRATIVE TECHNICIAN IN CLINICAL CENTER
ADMISSIONS.

JESSE J. FERGUSON, JR.

HER RELIABLE, EFFICIENT, ACCURATE WORK AS A LABORATORY TECHNICIAN HAS BEEN CRITICAL TO THE SUCCESS OF RESEARCH BY LEADING NIH SCIENTISTS OVER A 25 YEAR PERIOD.

SHE IS A BIOLOGICAL LABORATORY TECHNICIAN, LABORATORY OF BIOCHEMISTRY
DIVISION OF CANCER BIOLOGY AND DIAGNOSIS, NATIONAL CANCER
INSTITUTE.

RUTH B. GASTON

HE HAS PLAYED A ROLE IN THE HIGHLY USEFUL RESEARCH PLANNING REVIEWS AND IN DEVELOPING PRINCIPLES FOR STRENGTHENING NIH'S PLANNING CAPABILITIES.

HE IS CHIEF, PROGRAM PLANNING BRANCH, DIVISION OF PROGRAM ANALYSIS,
OFFICE OF PROGRAM PLANNING AND EVALUATION, OFFICE OF THE DIRECTOR.

KURT HABEL

HER EFFECTIVE SERVICE ON NUMEROUS NIH-WIDE COMMITTEES HAS FOSTERED EQUAL OPPORTUNITY AND ESSENTIAL CONTRIBUTIONS TO DEVELOPMENT OF THE NIH CHILD CARE PROGRAM.

SHE IS EQUAL EMPLOYMENT OPPORTUNITY SPECIALIST, NATIONAL
INSTITUTE OF DENTAL RESEARCH.

BARBARA Y. IBA

HER PIONEERING WORK IN DISCOVERY AND MAPPING OF COMPLEX GENES AND HER EXCEPTIONAL CONTRIBUTIONS AS A SCIENTIST HAVE EARNED INTERNATIONAL RECOGNITION AND THE RESPECT OF HER COLLEAGUES AT NIH.

SHE IS RESEARCH MICROBIOLOGIST, LABORATORY OF IMMUNOLOGY,
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.

ROSE LIEBERMAN

THIS INDIVIDUAL IS ADMIRER FOR LEADERSHIP, ABILITY AS A TEACHER, AND GENUINE CONCERN FOR PATIENTS AND FELLOW WORKERS.

HE IS CHIEF, DEVELOPMENTAL ENDOCRINOLOGY BRANCH, NATIONAL
INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT.

D. LYNN LORIALUX, M.D., PH.D.

HER ABLE SERVICES AS A PROFESSIONAL AND A PRECEPTOR HAVE BEEN CRITICAL TO NIH IN MAINTAINING ITS ROLE AS THE FOREMOST INNOVATOR IN CANCER NURSING.

SHE IS HEAD NURSE, UNIT 2B, NURSING DEPARTMENT, CLINICAL CENTER.

DORIS J. MARSHALL

HIS LEADERSHIP HAS INSTILLED STAFF AWARENESS AND RESPONSIVENESS IN DEALING WITH THE COMPLEX PROBLEMS BROUGHT ON BY THE VAST AMOUNT OF CONSTRUCTION WITHIN AND SURROUNDING THE CLINICAL CENTER.

HE IS THE CLINICAL CENTER'S CHIEF, ENVIRONMENTAL SANITATION CONTROL DEPARTMENT.

WALTER E. MOTEN

HER CAREER AT NIH IS AN EXAMPLE OF SUSTAINED EXCELLENCE, REFLECTING CREDIT ON HER, THE NATIONAL INSTITUTE OF DENTAL RESEARCH, AND THE NIH.

SHE IS CHIEF, CONTRACT MANAGEMENT SECTION OF THE DENTAL INSTITUTE.

EDITH W. MULLEN

HE HAS INSISTED ON MAXIMUM COMPETITION IN THE CONTRACT PROCESS AND VIGOROUS PROTECTION OF THE CONTRACT NEGOTIATION AND AWARD SYSTEM FOR THE NIH.

HE IS CHIEF, CONTRACT MANAGEMENT BRANCH, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.

LEWIS S. POLLACK

THIS INDIVIDUAL HAS PROVIDED SUBSTANTIAL CONTRIBUTIONS TO NIH ADMINISTRATION OF LABOR CONTRACTS AND SERVICE AS RESPECTED ADVISOR TO MANAGERS AND UNION OFFICIALS ALIKE.

SHE IS ACTING CHIEF, LABOR MANAGEMENT BRANCH, DIVISION OF PERSONNEL MANAGEMENT, OFFICE OF THE DIRECTOR.

GLORIA T. RILEY

THE IMMUNOLOGY AND CANCER CENTERS PROGRAMS OF THE NATIONAL CANCER INSTITUTE OWE MUCH TO HER EXTRAORDINARY ADMINISTRATIVE AND SECRETARIAL SKILLS.

SHE IS ADMINISTRATIVE ASSISTANT, DIVISION OF CANCER BIOLOGY AND DIAGNOSIS, NATIONAL CANCER INSTITUTE.

JANICE ROMANOFF

THIS INDIVIDUAL HAS MADE THE NIH PRESCHOOL A MODEL BY CREATING A LOVING, STIMULATING AND SECURE ENVIRONMENT FOR MANY CHILDREN OF NIH EMPLOYEES.

SHE IS DIRECTOR OF THE NIH PRESCHOOL.

SHERRIE RUDICK

THIS INDIVIDUAL IS AN ARTICULATE SPOKESMAN WHOSE SCIENTIFIC INSIGHT AND COMMITMENT TO RESEARCH ON DIABETES HAS ENHANCED AND UNITED THAT EFFORT WITHIN NIH AND AMONG OTHER FEDERAL AGENCIES.

HE IS ASSOCIATE DIRECTOR FOR DIABETES, ENDOCRINE, AND METABOLIC DISEASES, NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM AND DIGESTIVE DISEASES.

LESTER B. SALANS, M.D.

HER OUTSTANDING PERFORMANCE IN SUPERVISING A HIGHLY TECHNICAL "GERMFREE" OPERATION HAS SERVED BOTH INTRAMURAL AND EXTRAMURAL INVESTIGATORS AND HER DEDICATED HUMAN SERVICES, PARTICULARLY AS COUNSELOR, HAS BEEN BENEFICIAL FOR HANDICAPPED EMPLOYEES AT THE NIH.

SHE IS CHIEF, GNOTOBIOTICS UNIT, VETERINARY RESOURCES BRANCH, DIVISION OF RESEARCH SERVICES.

KATHLEEN I. SNOWDEN

SHE PERSONALLY REPRESENTS THE NIH WITH INTELLIGENCE, SENSITIVITY, AND UNFAILING COURTESY IN GREETING AND ESCORTING THE MANY INDIVIDUALS AND GROUPS WHO ARE OUR SPECIAL GUESTS AT THE CLINICAL CENTER.

SHE IS A PUBLIC INFORMATION SPECIALIST IN THE CLINICAL CENTER.

LINDA TRUITT

HER EXCEPTIONAL TALENTS HAVE BEEN USEFUL IN DEVELOPING A PROGRAM TO SUPPORT RESEARCH IN HUNTINGTON'S DISEASE AND RELATED DISORDERS IN THE INNOVATIVE "CENTERS WITHOUT WALLS".

SHE IS A HEALTH SCIENTIST ADMINISTRATOR, NEUROLOGICAL DISORDERS PROGRAM, NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE.

NANCY S. WEXLER, PH.D.

THIS IS A GROUP AWARD PARTICIPATED IN BY THREE EMPLOYEES IN THE OFFICE OF THE DIRECTOR:

AS MEMBERS OF THE "PROJECT TEAM" THEIR WISDOM AND SENSITIVITY ENLISTED THE ENTHUSIASTIC SUPPORT OF STAFF IN ENHANCING PRODUCTIVITY AND MORALE IN THE PRINTING AND REPRODUCTION BRANCH.

HE IS A WORK IMPROVEMENT CONSULTANT, DIVISION OF PERSONNEL MANAGEMENT.

LARRY BONNER

SHE IS AN EQUAL EMPLOYMENT OPPORTUNITY SPECIALIST, DIVISION OF ADMINISTRATIVE SERVICES.

DELORIS DOZIER

HE IS A MANAGEMENT ANALYST, DIVISION OF MANAGEMENT POLICY.

JERRY E. MOORE

BIOMEDICAL RESEARCH IN THE 1980s

DONALD S. FREDRICKSON, M.D.

THE new administration could be the most fiscally constrained in half a century, and yet it must endeavor to provide full support to a revolution. That is the best word to describe the present state of the biologic sciences. Their economic foundation, however, has rarely been more precarious.

Never has there been a comparable period of growth in the knowledge of living things. The current revolution in the life sciences is not a simple, linear projection of the growth curve in knowledge for the past century. A striking perturbation of that growth has occurred, amounting to a geometric progression of available information. Achievements of research in chemistry, physics, and many allied disciplines during this same period have led to new technologies contributing to a flood of discovery in biochemistry, physiology, and medicine. Our ignorance is still vast, but we are on the threshold of some unusual transformations in health practices, agriculture, and industry.

The major reason for all these events is the commitment of serious public support for research in the natural sciences. In the United States this commitment did not occur until a little over 30 years ago. Our example proved infectious to other affluent, developed countries, some of which had to reconstruct their science base after a devastating war.

Since 1950, approximately \$75 billion from private and public funds has been expended for research and development in health care in the United States. This investment represented 0.06 per cent of the gross national product in 1950 and 0.33 per cent in 1974; it has remained at about 0.31 per cent in the past few years. The contributors and participants have been in industry as well as the nonprofit sector. About 60 per cent of the total funds and an estimated 90 per cent of the basic research has been supported from the federal budget.

Over these three decades an unprecedented system of inquiry has grown up. It involves private and federal laboratories and nearly all universities. These institutions have adapted their structure and organization to incorporate greatly expanded scientific investigation as an essential part of the teaching function, to maintain the necessary replenishment of trained researchers, and to cope with the vast increase in the flow of information, synthesizing it into

knowledge and encouraging its diffusion and practical application.

Such scientific endeavor is of necessity largely an instrument of the state. Increasingly, weaknesses in the economies of America and the rest of the world have jeopardized the ability of governments to sustain the biologic revolution. We have the responsibility to alert the governors of our societies that one of our greatest intellectual adventures — one ultimately crucial to our survival — needs careful stewardship so that it will not wind down irreversibly.

STEP BACK 100 YEARS

For purposes of perspective, let us go back about 100 years. Pasteur had dispelled the myth of spontaneous generation of living things. Koch had risen among a generation of great pathologists and chemists in his country to set the rules for proving that an organism causes a particular disease. Modern physiology was under way with Claude Bernard. Laboratory experiments were beginning to shake up medical epistemology. The action was mainly confined to Britain and the European universities.

In America at the turn of the century, John D. Rockefeller's advisor picked up Osler's latest medical textbook. The art of descriptive medicine seemed to be high, but the impotence of the healing arts was unconcealed. He encouraged his patron to create the first medical-research institute in America in 1901. Simon Flexner, whose patron was Carnegie, soon determined how to force a marriage of medicine to science. Over 70 nonacademic proprietary medical schools were thus forcibly closed between 1910 and 1925. Rockefeller's funds also created clinical-science units, with a full-time physician-investigator in charge, at Johns Hopkins and then in London.

Then came the World Wars. The medical corps of the Allies and the Central Powers attended the victims of World War I with arsenicals and carbolic acid. They entered World War II with German sulfa and finished with British penicillin. At the end of this war, America emerged with its industries intact and in possession of nuclear power. Its government was persuaded to make a fateful investment: public support of scientific research in university and federal laboratories.

There was a special desire on the part of the Congress to have just one more war, this time against disease. A tiny federal agency, the National Institutes of Health (NIH), was given trusteeship for federal funds devoted to increasing knowledge of human biology and medicine. The growth of the NIH was prodigious.

From the National Institutes of Health. Address reprint requests to Dr. Fredrickson at Bldg. 1, Rm. 124, National Institutes of Health, Bethesda, MD 20205.

Adapted from a lecture presented on the occasion of the 50th anniversary of the Medical Research Society, at the Royal College of Physicians, London, December 12, 1980.

Its resources and its example of public support of science flowed to Britain, Europe, and Asia to revive the activities of older partners in a scientific universe in the process of rapid expansion.

THE GROWTH SPURT BEGINS

Let us take 1950 as a reference year. The pump oxygenator was used for the first time. A remarkable epoch in cardiology commenced, with diagnostics and surgery competing and combining to achieve mastery of the heart — one of the inviolate organs since ancient times. An artificial kidney was spinning in Boston. The recently available shipments of radioisotopes from Oak Ridge were setting in motion innumerable raids into the previously inaccessible interiors of intact organisms. Metabolic maps that once had taken a lifetime to trace were rapidly composed and disseminated.

Molecular biology was in its infancy, although evidence of the immortal secret of DNA had been unearthed in the 1940s. There was some rereading of the forgotten Croonian Lectures of Sir Archibald Garrod (1908). By mid-century the term "inborn errors of metabolism" could be rephrased to become "one mutant gene — one defective enzyme."

MOLECULAR DISEASE

The 1950s began with a revolutionary restatement of the hypothesis epitomized as "molecular disease." About 100 metabolic diseases were recognized to be of genetic origin. One of the first identifications of a specific enzyme deficiency was Gerty Cori's demonstration in 1952 that deficient glucose-6-phosphatase activity was an underlying factor in von Gierke's glycogen-storage disease. It had taken 50 years from the first case report to elucidate the cause.

By the end of the 1950s, a dozen such enzyme deficiencies had been clarified. Two of the four diseases that had been considered 40 years earlier in Garrod's classic writings were among them: alkaptonuria, reported at least 100 years before, and albinism, which had been described by Pliny.

The precise error in structure of the chain of amino acids dictated by a mutant gene was first exposed in this period. The sometimes fatal association of sickle cells with anemia had first been reported by a Chicago physician in 1910. New methods for separating globins by electrophoresis led to the hypothesis that a single amino acid substitution in hemoglobin S was involved (1949). Within a few years, the switch of one valine for a glutamic acid residue in a chain of 280 amino acids was uncovered (1956). This profound demonstration of how human misery can spring from so tiny a base marked an epochal expansion in the scale of our self-comprehension.

The list of genetic disorders in which the defective gene product is known grew from 15 in 1960 to over 1000 in 1980, and today we can identify the chromosomal location of more than 35 such mutant human

genes. It has been predicted that the entire human genome (more than 100,000 genes) may be mapped before the 21st century.

In the past two decades whole collections of pathologic processes have been lifted out of obscurity, with an accompanying illumination in physiology. An example was the conversion of the numerous and mysterious diseases of mucopolysaccharide and sphingolipid storage to specific acid-hydrolase deficiencies in the period from 1965 to 1975. Simultaneously, the normal scavenger system located in reticuloendothelial lysosomes suddenly emerged, complete with a catalog of the loci of potential malfunctions.

A timely mastery of the art of growing human cells in tissue culture permitted detection of abnormalities in the fetus and recognition of carrier states in potential parents. Enzyme defects can now be demonstrated in cultured skin fibroblasts for over 100 inborn errors of metabolism and in cultured lymphoblastoid cells for at least 25. Not one such enzymatic error could be so identified in 1960.

There has also arisen over the past 25 years a concept of genetic polymorphism that is invaluable for the understanding of protein differences in normal persons. Someday not too far off, all the proteins in the blood or organs will be identified and measured. This concept of allelism will greatly enhance our ability to determine hereditary variations in diseases and in individual adaptability to stress.

The structure of DNA (1953), the replication of genetic messages, the major features of their transcription and translation (by the mid-1960s), and the revelation of the genetic code all represent leaps in understanding that cannot be fully described here. The same fleeting mention must be made of the molecular vision acquired by science through numerous new tools. Now we can not only see organelles and cell surfaces but also comprehend the baroque beauty of multiple overlapping controls on enzyme activity and the demography of receptors and agonists that regulate a seemingly infinite number of metabolic processes.

Certainly, one should emphasize the applications of such research that have affected the lives of millions over these same 30 years — achievements such as hormonal contraception; eradication of smallpox by vaccination; control of polio, rubella and Rh disease by immunization; and the remarkable changes in mortality from cardiovascular disease.

GENETIC RECOMBINATION

In the early 1970s, the techniques for combining genes seemed the most exciting and provocative addition to the "new biology." We added to our bag of molecular images such desiderata as "sticky ends," circular plasmids, nose cones of insertable viral vectors, and a parade of imaginary genetic chimeras. At the time, some of us also had to cope with more tangible phenomena such as protests, guidelines for ex-

perimentation, and statements on environmental impact. As genetic recombination moved from a highly speculative curiosity to the basis of a new industry, we took lessons in public governance of science that will surely stand us in good stead in the 1980s.

In the years of exploration preceding emergence of this startling technology, the public also amortized costs of research and development that no industrial conglomerate could have programmed or underwritten. These new means for producing valuable biologic materials promise great economic return. The costs of development, however, have already been repaid in fundamental information about gene structure and control that only the pure proteins or polynucleotides produced by the unicellular factories could provide.

Methods of genetic recombination and techniques for rapid determination of the sequential structure of genes resulted in Nobel Prizes in 1979 and 1980. Few discoveries have been so promptly rewarded, and few have projected us so fast into the future. Yet the 1980 Nobel Prizes also recognized spectacular achievement in quite another sector of biology.

MONOCLONAL IMMORTALITY

The 1980 Nobel Prize in Physiology or Medicine was awarded for the discovery of the major histocompatibility complex (MHC).

The MHC is far from being completely understood. It appears to be a "super-gene," of which a well-explored region is the major regulator of the immune response to foreign substances or antigens. It controls the interactions of different classes of lymphocytes with one another and with scavenger cells, and it regulates the interaction of these cells with antigens. The rapidly unfolding story of the immune system boggles the mind. In it lie the bases for resistance to infections and for rejection of grafts. Doubtless, immunology holds secrets of the cause of cancer and resistance to it. Disorders, such as multiple sclerosis, juvenile diabetes mellitus, systemic lupus erythematosus, and other rheumatic conditions are also mysteriously associated with certain recognition antigens on the surface of cells — antigens located under the directions of the super-gene MHC.

The growth phases in our knowledge of immunology have followed the time phases of disciplines already mentioned, although the affinity of an antibody for an antigen has long been one of the most important tools for sensitive, highly specific identification and quantification of substances. In the past dozen years, Nobel Prizes have been awarded for the development of radioimmunoassays and for the elucidation of the complex structure of antibodies. Remarkable progress has recently been made in differentiation of the roles of lymphocytes.

Multiple B-lymphocyte clones respond to introduction of an immunizing agent in the body by producing antibodies directed against the antigens. Each responding lymphocyte clone produces identical anti-

bodies to one of the antigenic determinants. The result is a mix of closely similar antibodies that hunt down the antigens and selectively bind to them. Other T lymphocytes, communicating through chemical messages, either induce the B cells to respond to antigens or keep them from doing so. Some T lymphocytes become "killer cells" capable of destroying other cells.

Immunology has not only gone molecular; in the development of the hybridoma, it has perhaps discovered perpetual motion. Five years ago a procedure was described that consists of fusing in culture a myeloma cell (a plasma cell that has been malignantly transformed into an uncontrollable immunoglobulin secretor) with single lymphocytes immunized to produce specific antibody. The resulting hybridoma thus confers the immortality of the myeloma cell on the secreting lymphocyte. Under appropriate conditions, these fused cells yield clones of lymphocytes that emit monoclonal antibodies. The secretors can be maintained permanently in culture, each producing large amounts of antibody to a single antigenic determinant.

The myeloma cell, or "permissive horse," when provided with the desired template, becomes a remarkable mammalian cell-cloning vehicle. It is comparable to a host bacterium, such as *Escherichia coli* K12, as used in recombinant technology, into which has been inserted the appropriate genetic messages for continuous production of a foreign protein or polynucleotide. If one imagines a combination of the bacteria to produce genetic programs for antibodies and the hybridomas to make the products, a library containing the 10 million or so potential human antibodies is within grasp — an incomparable collection of tools if some means can be devised to make them readily accessible.

NEW MEDICAL MAGIC

The exquisite specificity of antibodies, which lies in the vast number of structural permutations that are programmable in the "hypervariability" portion of the antibody molecules, provides the capability for targeting messages to a single cell in the body. There are some researchers who contemplate making an antibody with an affinity for certain cancer cells and conjugating it with a drug — say, a molecule of ricin, a castor-bean poison so powerful that one molecule can kill a cell. Others are busy purifying human killer T lymphocytes directed to recognize only specific metastatic tumor cells. Unleashed into the circulation, the killer cells are expected to seek out their targets and to devour them selectively.

Recombinant-DNA technology is ideally adapted to producing large amounts of pure antigens for use in vaccines. The days of sensitizing protein impurities in commercial vaccines may be gone. Doors are also opening that lead to vaccine control of some protozoan infections, perhaps including malaria, the

world's greatest killer, or Chagas' disease, the scourge of Latin America. The new technology may have inestimable value in providing antigens or antibodies to use against these age-old enemies.

Let us pass over other opportunities for obtaining new knowledge — interferons and how they thwart viral infections or the study of cell transformation in the malignant process — and give one more example of the revolution.

Modern electronics has put us in awe of the numerous transistors connected in a single chip so that an almost infinite number of computer programs can be accommodated. The microcircuitry of the brain and its programming to achieve the very-large-scale integration of higher neurologic function is much more complex and romantic.

Over a period of 30 years, separate discoveries have coalesced to reveal the structure of the brain. Molecular visions of the chemical anatomy and bioelectric integration of the circuitry of the nervous system are now emerging. It is no longer news that the discharge of the neurons is both initiated by and productive of chemical neurotransmitters. The recent elucidation of how numerous kinds of neurotransmitters play upon specific receptors around the body of the neuron to regulate its electrical activity is indeed news, if one has not been keeping close tabs on developments.

Different classes of neurotransmitters — those derived from norepinephrine (such as dopamine), amino acids (such as gamma-aminobutyric acid), or polypeptides (such as the endorphins) — have been identified with great specificity, and their structures have been described in detail. The regulation of the sensitivity of their receptors is becoming clearer, as are the mechanisms by which each finally acts on the neuron to regulate its electrical potential. The firing of each nerve — an impulse releasing neurotransmitter at the next nerve synapse — is governed by multiple influences.

With this greater fundamental knowledge has come a comparable growth in concepts of nervous-system dysfunction and its treatment through safe and reasonable methods. The effect of lithium, which was serendipitously discovered in 1949, and of other tranquilizers, such as the benzodiazepines introduced in 1960, have markedly changed the management of mental disturbance. The mechanisms of action of these powerful drugs are now known in considerable detail. It will not be too long before the affective disorders, with their curious rhythms and awful intensity, can be better controlled through knowledge based on this kind of molecular dissection. Other mental disorders, especially those with genetically determined components, will similarly come within the reach of the therapist.

As these examples illustrate, the limits to our conquest of the mysteries about us have been radically displaced. Little of the unknown in the physical realm seems to be ultimately unconquerable if the inquiry is sustained.

However, there are unmistakable threats to the size and vigor of scientific inquiry today. Monetary inflation, decreased growth of industrial productivity, and critical shortages in energy are seriously and continuously undermining the affluence of all the developed countries in which scientific research has thrived.

The situation might be viewed in the context of the activities of the National Institutes of Health. The NIH began in 1887 as a modest public-health laboratory on Staten Island, N.Y. In 1937 it was relocated in Bethesda, Md., with a newly created National Cancer Institute.

In 1948 enthusiasm for peacetime continuation of federal support for health research resulted in the formation of additional institutes. The National Heart Institute, the National Dental Institute, and the National Institute of Mental Health were established next. (The National Institute of Mental Health left the NIH in 1967 and is now part of the Alcohol, Drug Abuse, and Mental Health Administration. Its intramural research activities remain on the NIH campus in Bethesda. Data presented here do not include the resources of the Alcohol, Drug Abuse, and Mental Health Administration.) Eight other institutes were later established, and the aggregate NIH was on its way to becoming the single largest supporter and conductor of research in medicine and the life sciences that the world has seen — or, conceivably, may ever see again, depending on the fortunes of the American economy in the years ahead.

The annual NIH budget grew almost exponentially, expanding 13-fold between 1956 and 1966 (Fig. 1). Even after the dramatic rate of growth had declined, the separate appropriations for some institutes continued to increase. Obligations for all institutes totaled \$3.2 billion in fiscal year 1979. It is possible that this sum may have been a high-water mark in purchasing power. In constant (1969) dollars, it was equivalent to \$1.62 billion — a 49 per cent increase

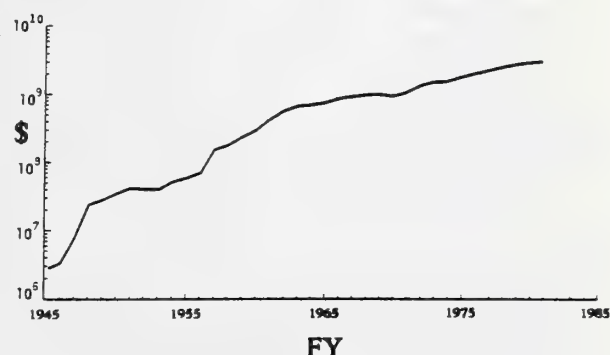


Figure 1. Congressional Appropriations for the National Institutes of Health, Fiscal Years 1945 through 1981.

Aggregate appropriations rose from a total of under \$2 million in 1945 to \$3,616 million for 1981. As shown on this semi-log scale, the rate of increase was steepest in the early years. (In 1957 the program doubled.)

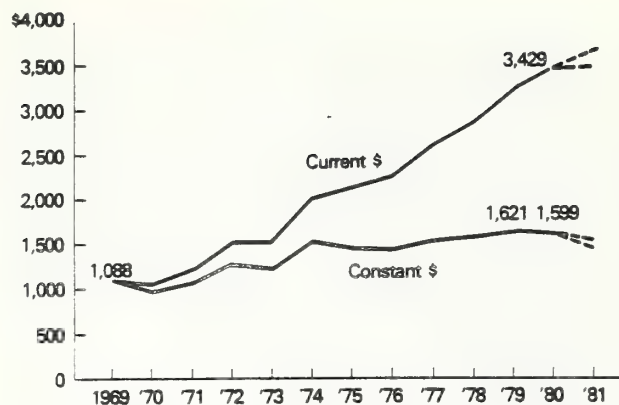


Figure 2. Obligations of the NIH in Current and Constant (1969) Dollars.

Obligated funds for the aggregate of NIH programs are shown for fiscal years 1969 through 1980, with alternate projections for fiscal 1981. In terms of constant dollars, the high point is 1979. Even the higher projection for 1981 (which has proved to be accurate) represents a decline in the purchasing power of 5.5 per cent, according to a price index for biomedical research and development.

over 1969 (Fig. 2). Since 1979, however, the tide has turned. The Congress, engaged in a struggle to set budget ceilings for itself, never passed an appropriation for the Department of Health and Human Services (DHHS) for fiscal year 1980, and the stopgap "continuing resolution" included \$1.6 billion (1969 dollars) for the NIH.

One could easily fail to understand the competition for funds for research if one sees that the NIH budget represents only a small fraction (less than 2 per cent) of the huge budget of DHHS (\$195 billion in 1980). Yet all but \$11 billion of the departmental budget consists of fixed entitlements for health and welfare. The budget of NIH was one third of the residual — "controllable" — fraction!

The 96th Congress also failed to pass an appropriation for fiscal year 1981. On its final day it approved a continuing resolution through June 1981, which brought the NIH budget to a projected annual figure of \$3.6 billion, or \$1.53 billion in 1969 dollars. This amount represents a decrease of approximately 5 per cent in purchasing power from the 1979 level. President Carter, in his budget message of January 15, 1981, proposed a rescission of \$50 million from the continuing resolution level. His proposal for NIH for 1982 was \$3.85 billion (an estimated \$1.49 billion in 1969 dollars).

The distribution of NIH support can be plotted on numerous axes. In one projection it is spread over categorical regions (related to organ systems and other diseases) and nonclinical disciplines that provide tools to help to reduce problems of biology and behavior to the more manageable molecular terms. These elements of the NIH are known as the BIDs (bureaus, institutes, and divisions), and 14 of them have separate appropriations individually defended in

Congressional hearings. This projection of activities (Fig. 3) thus reflects the one preferred by the Congress in its oversight of health research.

One of the most useful ways to examine the aggregate of NIH activities is to distribute them serially from a less differentiated "science base" through the stages by which discoveries proceed to practical applications (Fig. 4). This examination includes clinical trials, the transfer of useful inventions into practice, and some continued sorting through the doctor's bag to help decide what should be discarded. It is axiomatic that research activities must also include the training of scientists. I believe that the amount of training now subsidized is the minimum desirable fraction of federal support for health research.

COMMUNAL RESOURCES

Today's international biomedical-research system has a high dependence on certain resources and services, some of them maintained through co-funding or other cooperative means on an international basis. The National Library of Medicine in Bethesda is the world's principal curator for biomedical-research information. Nearly every country uses and contributes to its programs for data collection and retrieval. The demands for data management are rising rapidly, and new technical gains introduce marked jumps in need. For example, the accelerated ability to determine the structure of polynucleotides (including genes, messenger RNA, and viruses) is producing a stream of data that must be stored and made accessible so that its rich content of new knowledge can be efficiently used.

Biomedical science, represented by institutions supported by the NIH and the National Science Foundation in the United States and by the medical-research councils and similar organizations abroad, is also the curator of other kinds of living information. A huge inventory of organisms and other cell lines represents a priceless and irreplaceable chain. It grows daily, and so does the task and the cost of maintaining access to its components.

The NIH maintains a total of about 1200 beds for clinical investigation. Five hundred are at the Clinical Center in Bethesda, and the rest are grant supported. As hospital costs rise and constraints on use of facilities become more severe, much clinical investigation can only be conducted in units specially set aside for it. As clinical care and medical research increasingly involve ambulatory and often normal subjects, facilities for handling observations of these populations will become more and more important in the 1980s.

The NIH runs seven large primate centers. These centers are important not only for the research they do but also for breeding to replenish the dwindling world supply of valuable research animals. The installation and maintenance of large equipment such as scanning electron microscopes, electron probes, mass spectrometers, and many specialized data-manage-

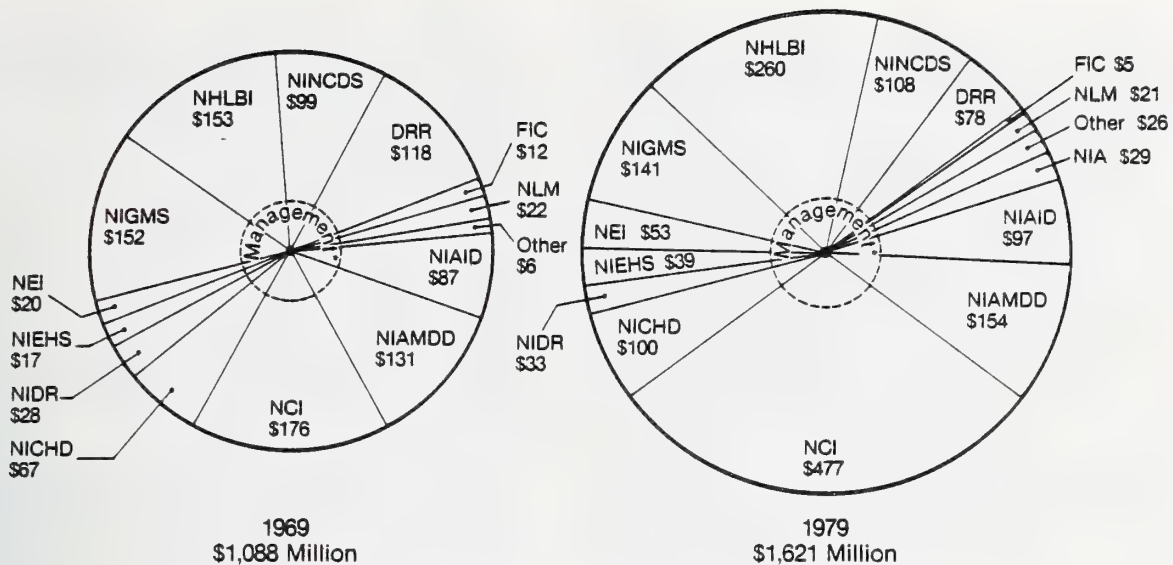


Figure 3. Obligations of the NIH by Program, 1969 and 1979, in Constant (1969) Dollars.

The institutes and research divisions of NIH accounted for \$3,185 million in 1979, which represents \$1,621 million in 1969 purchasing power.

The National Cancer Institute (NCI) shows a 171 per cent increase in constant dollars, while the Division of Research Resources (DRR, which contains the biomedical research support grants program) and the National Institute of General Medical Sciences (NIGMS, which contains a high proportion of NIH training programs) declined by 34 and 7 per cent, respectively. NIAID denotes National Institute of Allergy and Infectious Diseases; NIAMDD Arthritis, Metabolism, and Digestive Diseases; NICHHD Child Health and Human Development; NIDR Dental Research; NIEHS Environmental Health Sciences; NEI Eye; NHLBI Heart, Lung, and Blood; NINCDS Neurological and Communicative Disorders and Stroke; FIC Fogarty International Center; NLM National Library of Medicine; and NIA National Institute on Aging.

*The costs of the Office of the Director and buildings and facilities are included here as costs of management.

ment systems are other examples of communal resources to be accommodated in each year's budget.

INVESTIGATOR-INITIATED RESEARCH

The most important scientific discoveries are made by investigators pursuing their own ideas. In competition for support, they are willing to set forth their hypotheses and the methods that they would use to test them. Once support is committed, it should be guaranteed for a reasonable period, and the scientists should be given latitude to adapt their methods to overcome unexpected barriers. In support of research by NIH, evaluation is both prospective and retrospective, and the whole enterprise is kept accountable by peer recognition and review. Under the prevailing strict and uncompromising arrangements, one must produce to stay in the system.

Most of the research that NIH supports is maintained through grants. A grant of the means to pursue new knowledge is different from a procurement contract, under which some kinds of scientific research and development are conducted. Among grants there are many distinctions. The largest share of NIH-sponsored, investigator-initiated research is supported by the "research-project grants" shown in Figure 4. A little over 16,000 such grants are in effect at any one time. The project grant is a commitment to support one or more scientists for a period of time, which now averages 3.5 years. In each fiscal year these continuing commitments are met first, and appli-

cants for renewal of their expiring grants join those submitting new proposals in competing for the remaining project-grant funds.

Since the total number of grants in the portfolio of a given institute reflects several cumulative years of

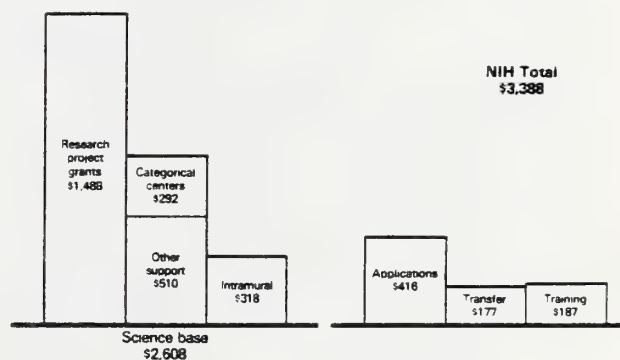


Figure 4. Distribution of NIH Funds, Fiscal Year 1980.

Congressional appropriations totaled \$3,388 million (1980 column of 1981 President's budget). It is useful to distribute the research budget in terms of "SATT" — science base, applications, technology transfer, and training. The science base is further divided into investigator-initiated project grants, categorical research centers and other support, including research resources, and the intramural program, mainly at Bethesda. Research-project grants to scientists in non-federal laboratories and clinics constitute 44 per cent of NIH funds. Such grants include traditional research grants and program project grants.

funding, the "new and competing" awards made each year are subject to considerable change. The 1975 level (4600) fell in 1976 to 3460, rose in 1978 to 5200 and again in 1979 to 5900, and was fixed at 4800 in 1980.

Another source of instability is inflation, which has recently outrun budget projections. The average annual cost of a project grant was \$88,000 in fiscal 1979, \$99,000 in 1980, and an estimated \$108,000 for 1981. The total number of new and competing awards that are fundable is also affected by rises in indirect costs — the administrative and overhead costs of sustaining the research enterprise — that the scientist's institution can recover from the federal government. These rises now average more than 27 per cent of the cost of the grant.

The resources available for competing awards are affected by the many interests that must be accommodated by the institutes in preparing the federal budget and arriving at congressional appropriations. The 96th Congress, for example, debated budget levels (Fig. 2) that represented capacities to fund competing grants in fiscal 1981 in numbers varying from 3800 to 5000. These two projected numbers of grants represent an alarming difference. At the level of 3800 awards, an average of only one in four approved competing grant proposals would be fundable. The immediate effect would be to deprive over 1000 productive scientists competing for renewal during the year of the drop.

STRIVING FOR STABILITY

Such prospects have led us to search over the past five years for ways to seek stabilization and to set priorities in anticipation of austerity. The share of NIH research dollars for investigator-initiated research through research-project grants has been preferentially protected, whereas the shares going to clinical trials, developmental work under contract, categorical research centers, communal resources, control programs, and other forms of scientific endeavor have declined. An initiative for stabilization of the funding of project grants has had the endorsement of most of the health-research community. In the 1980 budget, the Administration agreed to request funds for approximately 5000 competing grants, and Congress appropriated that amount. Although President Carter twice found it necessary to reduce his 1981 budget, the 5000 grants survived both reductions. Congress ultimately included funds for the 5000 in the continuing resolution for fiscal 1981.

The willingness of the executive and legislative branches to support the principle of stabilization through these recent difficult years is a dramatic gesture toward continued public support of the biologic revolution.

RECRUITMENT TO SCIENCE

In the long term, the most devastating of the effects of financial instability is the discouragement of the

young from entering scientific research. It is a profession with a "high metabolic rate." The best NIH figures suggest a loss of up to 10 per cent of the scientists whom we support each year. In the United States, this loss can mean something on the order of 2000 principal investigators. There is inadequate information to explain this turnover. Some of it is due to loss of scientists to teaching, administration, or industry, and some of it to failure to compete successfully for renewed support. Whatever the reason for this turnover, a continuing tide of young people moving into research is crucial to the vitality of science. Their hands perform much of the research. Their enthusiastic curiosity is the oxygen required to keep the flame bright.

The federal government now supports some of the training of more than 50 per cent of the workers who are awarded NIH research grants. Training awards were introduced early (1938) as part of the NIH research program. For about 20 years, NIH grants and fellowships had perhaps the greatest influence of all federal programs on the organization and curriculum of the academic medical centers. They also provided the bulk of the American scientists who helped create the revolution in biology. The numbers of trainees maintained by the NIH on training grants and fellowships today is about half the number supported in 1965.

THE DWINDLING BEDSIDE CONNECTION

A disturbing feature has been added to the problems of replacement of scientists in the existing system of inquiry; it confronts biomedical research not only in America but in the rest of the world as well. Physicians and dentists are losing interest in being clinical investigators. The number of physicians seeking postdoctoral research training is declining, according to all available indexes (Fig. 5). The reasons for this decline are complex and include the indebt-

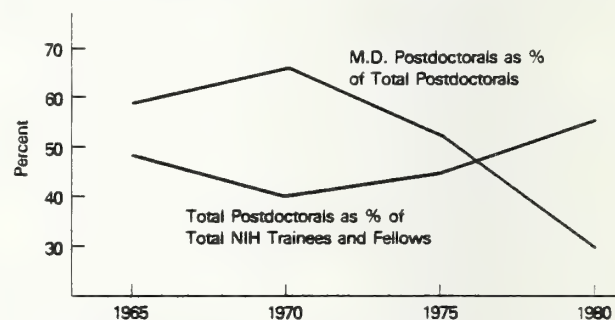


Figure 5. Percentages of Postdoctoral Trainees and Fellows and of Physician Postdoctoral Researchers, NIH, 1965 through 1980.

The total number of NIH trainees and fellows declined from 18,945 in 1965 to an estimated 10,284 in 1980. Over this period, total postdoctoral trainees, although declining in number, rose as a per cent of all trainees (48 to 55 per cent). Physician postdoctoral researchers, however, declined in both number and per cent (59 to 30 per cent) of all postdoctoral researchers.

edness amassed by many physicians in qualifying for their medical degrees, the higher percentage of graduates who are married, the economic disadvantages of academic employment, the contemporary interest in primary care, and the ascendance of life styles that are incompatible with spending weekends in the laboratory.

Another important reason is the changing demands made by science itself. The pace of advance is now so fast, and the shifts in required technology so frequent, that to be a first-rate scientist in addition to being a well-qualified medical specialist requires painful straddling of divergent ambitions. Students in the upper reaches of medical-school classes generally will not compromise with excellence in whatever they do. Therefore, in the 1980s the ranks of medical research will be increasingly filled by scientists who are not medically trained. We will need better training for nonmedical doctorates of a sort that will broaden perspectives in human biology and provide greater access and interest in paraclinical research.

PUBLIC RESEARCH AND PRIVATE PROFIT

The profits of the Industrial Revolution have made possible the biologic one. Conversely, technologic exploitation of discoveries from biomedical research has repaid part of that debt by revitalizing industries.

Thanks to biomedical research on proteolytic enzymes, proteins no longer precipitate in beer. My sources thus credit to such research the development of the canned and bottled-beer industry. Similarly, basic enzyme research has contributed technology to the billion-dollar laundry-detergent business. From studies on the preservation of biologic materials has come lyophilization, or freeze-drying — now a major procedure in the preparation of instant coffee and other food products. Structural studies of complex carbohydrates have led to the manufacture of bonded starches resistant to amylase, and these compounds are the most important stabilizers now employed in the food industry to extend the shelf life of food products. Even the drive to microminiaturization within the electronics industry is profitably exploiting our fundamental knowledge about lipid membranes.

If much of this profit-taking from adaptations of research far removed from the biomedical starting point has been obscure, the recent emergence of many professors of biochemistry as corporate executives has not escaped notice. The rush of investment capital into recombinant-DNA technology and the isolation or production of interferons, which are likely to be followed soon by commercialization of antibody production, represents a new wave of industrial exploitation of the more recent discoveries in biology. Much of the intensity is derived from a recent Supreme Court decision that new forms of life are patentable.

Celebration of this success should be tempered by concern for three unpleasant side effects that it will bring to biomedical research in the 1980s. Perhaps the

most superficial of these effects will be a tendency to forget that much of the basic research on which profitable development depends cannot be supported by industry or any other private sources. It is therefore alarming to hear sanguine expressions of confidence that private patrons would come forth to support all worthwhile scientific research if the federal government withdrew. One is reminded of the dismal failure of the National Research Fund, which was established in 1926 to channel industrial funds into basic research. A goal of \$20 million over a 10-year period was set, but less than 2 per cent of that amount was received by 1930. Four years later, \$356,402 was returned to the contributors.

A second source of unhappiness may be the unmet need for clinical investigators. This shortage has a bearing on the recent flood of private capital into biotechnology. It is obvious that assessment of safety and efficacy will be an essential step before profits can be realized from interferons, specific antibodies, or other biologic agents prepared in new ways. No industrial combine can or should undertake all the clinical trials that will be required. Moreover, potential conflicts of interest will make it necessary for many clinical experiments to be publicly supported.

In the long view, the ability of the academic wing of the scientific community to deal with the increased temptations of profit will be a severe test of biomedical research in the 1980s. The recent decision by Harvard University not to exploit recombinant technology for profit was important, for although Harvard is the university most able financially to forgo such investment, it would also have been the institution most widely imitated if it had so invested. One is always being reminded that chemists or scientist-engineers have managed to survive in ventures that have become excessively proprietary, but has their science maintained its excitement and pace with greater commercialization?

We have only just learned how unlimited freedom of communication — making possible the most rapid and complete synthesis of experiences into wisdom — has allowed us to pass through the period of anxiety over recombinant-DNA technology without any evident harm to science or the world. Secrecy in science is anathema. Biology, as the science of life itself, is under special ethical constraints to remain as free as possible, and thus open and preeminently humane.

THE ZERO-SUM BALANCE

Biomedical research in the 1980s will require as much creativity in adapting to austerity as was evident in the period of maximum growth. When reallocation of resources becomes a zero-sum game, some of the rules need to be modified. All players must suppress narrow interests to the degree necessary to maintain the whole of the enterprise in balance with

respect to several key equilibriums: selective growth in areas in which scientific opportunity is hottest and persistent activity in colder areas in which need of knowledge is still great; highly categorical programming and the provision of communal resources with broader institutional support; the need for continuing quality control by competitive review and the longer-term investments merited by scientists of proved productivity; and a full continuum of activities from the most fundamental to the most practical ends of biomedical research.

The allocations of NIH resources shown in Figures 3 and 4 do not necessarily represent a perfect harmony of the balances just described. The categorical distributions (Fig. 3) shown for 1969 and 1979 reflect the play of scientific, social, and political factors. Because each institute supports fairly broad basic research as well as its categorical activities, adjustment to the ever asymmetrical nature of scientific opportunity is better than a superficial view of the situation might suggest.

Nevertheless, the distribution of resources needs to be frequently and systematically tuned. There is a requirement for a continuing technical and collegial process for setting (or at least recommending) priorities for allocations within the vast area covered by all the institutes. The Administration and the Congress clearly have final powers and responsibilities for these determinations. Their task can be aided by analyses emphasizing aggregate distributions of activities, represented in Figure 4. They have recently adopted such a global view in endorsing and supporting the move toward the stabilization of one portion of the resource allocation — the annual number of competing research-project awards. The next steps involve similar attention to the other essential elements of research support and the balance among them. For some of these elements, we have already reached the limit of sacrifice for maintaining the ability to award project grants.

SCIENCE AND ACADEMIC NEEDS

Necessary economies in public spending for research in the 1980s may also create some especially difficult challenges for educational institutions. We have come to think of teaching hospitals as different from the ordinary kind. Now we hear talk of "research universities." Few of us were alive when the healing arts were learned in places that had no laboratories beyond the abattoir, no libraries but a shelf of old texts and proprietary pamphlets, and no bridges to connect the questions raised by illness to the answers lying in research. The health sciences have led the healing arts out of dark empiricism, and there must be no retreat.

The same is true for the university's need for an intimacy between scientific inquiry and teaching. Again, the highly categorical project orientation of the NIH places the universities in jeopardy when teacher-researchers in the faculty lose their grants.

If the biologic revolution, now so well launched, is to be sustained through the 1980s and beyond, a *sine qua non* is increased attention to the government-university interaction in science. From the beginning, there has been a partnership of mutual need and support. Yet strains and misunderstandings abound and add to the problem of shrinking resources. In the 1980s, the NIH, the layers of government above it, and the members of the academic-science community must consult and work together to keep the partnership whole. Three aims in particular warrant careful examination: ensuring continued strength in the research capacity of the academic partners; attaining reasonable accountability in the use of public funds for science, without an excessive burden of accounting; and establishing basic concepts of cost sharing between the government and the university.

A sound partnership will temper the effects of economic stresses on the realization of the unparalleled opportunity in the health sciences.

ERRATUM

Biomedical Research in the 1980s (1981; 304:509-17). On page 509 under the heading "Step Back 100 Years," the seventh line in the second paragraph should refer to Abraham Flexner, not Simon.

Excerpts from



Proceedings
of the 1981
Meetings of the
Chairpersons
of NIH Scientific
Review Groups

Prepared by:
Division of Research Grants

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I. INTRODUCTION

In the late fall of 1979, the Associate Director for Extramural Research and Training, NIH, scheduled a series of meetings between representatives of the NIH administration and the chairpersons of the NIH scientific review groups. These meetings provided a forum for the chairpersons to voice their concerns about, and suggest refinements of, the peer review system.

From the viewpoint of the NIH, those meetings were highly productive, and so two additional Chairpersons meetings were held on February 9 and 17, 1981. To have an atmosphere conducive to free discussion, the one-day meetings were limited to approximately 25 participants. Further meetings are planned for 1982.

Besides the chairpersons, the following NIH representatives attended the meetings: Dr. Donald S. Fredrickson, Director; Dr. William F. Raub, Associate Director for Extramural Research and Training; Dr. Carl D. Douglass, Director, Division of Research Grants; Dr. S. Stephen Schiaffino, Deputy Director, Division of Research Grants; Dr. Charles R. McCarthy, Director, Office for Protection from Research Risks; Mr. Steven C. Bernard, Acting Grants Policy Officer; Mr. Richard J. Riseberg, Legal Advisor; executive secretaries of the scientific review groups; and administrators from the Bureaus, Institutes, and Divisions. A complete list of the participants is included in Appendix A.

The agenda for the meetings was as follows:

- 10:00 a.m. to 10:10 a.m.
Welcome and Introduction, Drs. Raub and Douglass
- 10:10 a.m. to 11:15 a.m.
Roundtable Discussion, Drs. Raub, Douglass, Schiaffino, and Chairpersons
- 11:15 a.m. to 11:45 a.m.
Regulations Regarding Human and Animal Subjects Involved in Research, Dr. McCarthy
- 11:45 a.m. to 12:30 p.m.
Impact of Office of Management and Budget, Circular A-21 ("Cost Principles for Educational Institutions"), Mr. Bernard
- 12:30 p.m. to 1:30 p.m. -- Lunch
- 1:30 p.m. to 2:10 p.m.
Allocation of NIH Resources, Dr. Fredrickson
- 2:10 p.m. to 2:30 p.m.
Debarment Regulations, Mr. Riseberg
- 2:30 p.m. to 3:30 p.m.
Roundtable Discussion, Drs. Raub, Douglass, Schiaffino, and Chairpersons
- 3:30 p.m. - Adjournment

Discussion items were chosen from topics of interest that had previously been solicited from the chairpersons and other scientific review group members.

To avoid repetition and to clarify the presentation, we have merged the proceedings from both meetings into one volume. For the same reasons, we have organized the unstructured roundtable discussions into subject areas. Finally, because it was impossible to identify most of the speakers, we have generally divided the roundtable discussions into anonymous comments or questions from the chairpersons and responses from the NIH Staff.

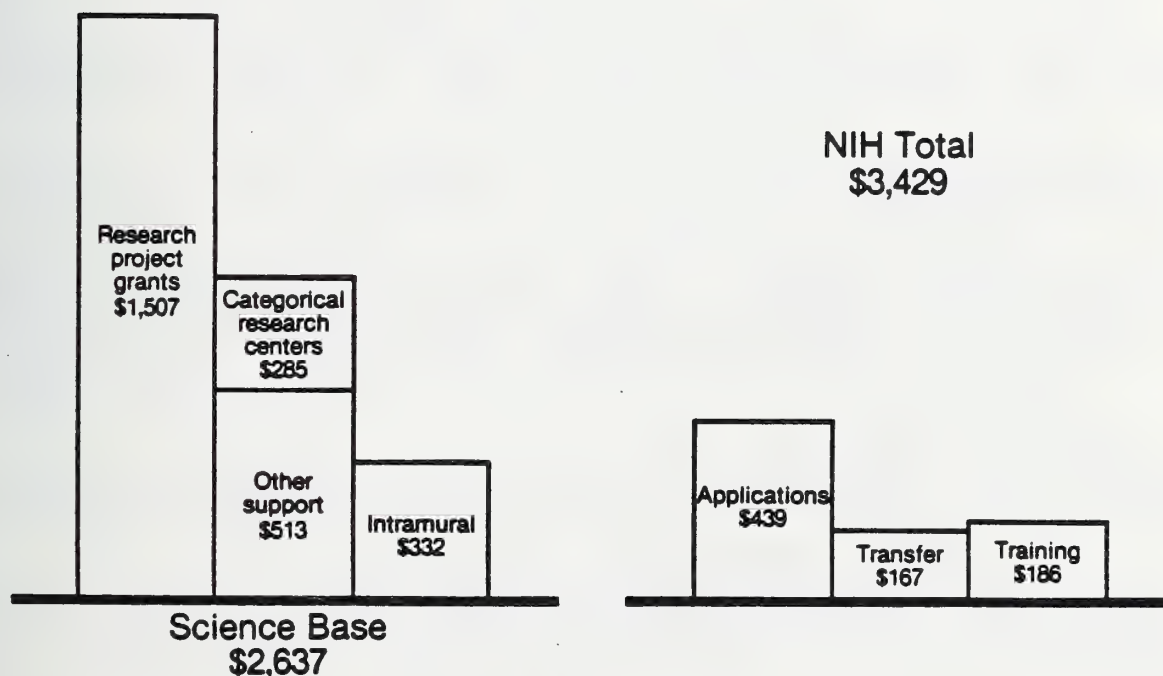
II. ALLOCATION OF NIH RESOURCES
Dr. Donald S. Fredrickson, Director, NIH

Welcome, all of you, to this roundtable. These meetings of chairpersons have become important parts of the NIH calendar, and they have never been more useful than they are today. I think it would help if I explained some of the macroeconomics of NIH. It may help answer some questions in the minds of many people concerned with support of biomedical research.

This slide (Figure 1) is what we call a SATT diagram. SATT stands for Science base, Applications, Transfer, and Training activities. Let me tell you how this NIH resource allocation is now used by us in budget planning.

Figure 1

DISTRIBUTION OF NIH OBLIGATIONS, FY 1980
(IN MILLIONS)



Thinking about austerity is not new for NIH. We've been watching the trends in both Administration and Congressional support for health research for some time--long before NIH passed its 1979 peak in budgeted purchasing power, \$3.18 billion (equivalent to \$1.62 billion in 1969 dollars). For at least a decade there has been a serious discontinuity between what the Administration has

proposed for NIH and what the Congress has finally appropriated. The Administration had often chosen to present to Congress the budget of the previous year, and Congress had reciprocated by adding enough to go beyond the costs of inflation, often plus increases for programs of special interest to it. These "disease," or "categorical," mandates often were resultants of political, social, and scientific forces and sometimes produced uncomfortable distortions in the budget.

Beginning in 1978-79, because of coming economic strains, the Congress began to experiment with a budget on itself. This meant that there might be a time when Congress might no longer be able to increase the NIH budget without an indication that the Administration was also desirous of doing so.

So at that time we began seriously planning for what might be a different trend in budgeting and appropriations, one seeking a common desire on the part of the Administration and Congress for stabilization of research support. In 1978 we had a conference here on the support of health research, which came out of a speech that then-Secretary Califano made. We searched in a serious way for consensus among many people about state support of science, and particularly the health sciences.

There emerged from this discussion agreement that the most important single aspect of research support is investigator-initiated research, under program project or research project grants. This became a first mandate, the highest priority to defend. But we also recognized that investigator-initiated research was only one part of a health research continuum, running from undifferentiated research to the practical inventions that make a difference in the quality of life and in the cost of health care.

In the strategy of planning for the future we concentrated on the aggregate disposition of NIH resources instead of the distribution within certain single mechanisms among the 15 line-item appropriations that make up the NIH budget. In the intense competition for Federal resources, we deal with highly structured committees in the Congress, and other complex processes within the Office of Management and Budget, the Administration, and its departments. The Budget has its own life. We have to understand it, use its language, change it slowly and in a sound way.

Across the NIH budget lines submitted to Congress every year there is a line called research project grants. This has always been an area of greatest Congressional interest. We decided to concentrate upon this particular line as the best expression of investigator-initiated research. Research project grants include mainly R01* and P01* grants, with which most of you deal, and the R23s*, small in monetary terms, but also important in providing early career opportunities.

* R01 - Research project grant
 P01 - Program project grant
 R23 - New Investigator Research Award

While NIH supports only about 40 percent of the health science in this country, it supports closer to 90 percent of the basic research. There are no alternative sources for funding most of this basic research. While research project grants are the largest single identifiable unit of the means to support basic science, there are several other important units identified in the SATT diagram under "Science Base."

The middle one, research centers and resources, is a mixture. There are center, mostly "core," grants, for which ROIs and POIs nowadays tend to provide more and more of the individual project support. In addition to the categorical centers, there are RCDAs* and the "communal resources" provided through the Division of Research Resources. It is sometimes forgotten how support for instruments, for clinical research centers, or for certain other functions that are universally needed by scientific institutions must be attended to by the non-categorical divisions of NIH. You can't expect people intent on doing something about heart disease or cancer today to be too concerned about the National Library of Medicine tomorrow or the large collections of biological specimens and data which must be maintained to form a chain from past generations into the future. For example, soon we're going to have to put a lot of money into a data base from polynucleotide sequencing, or we'll be stifled by data and lose efficiency in the use of new technologies.

Finally, the intramural part of science base, too, must be examined very carefully; its fortunes must also rise and fall as does the total system.

The "Applications" bar on SATT includes a variety of things. Most of the contract programs are there, as well as grants for development, an area where discoveries and inventions are being moved on toward more practical terms. Also included are many large clinical trials. Some people think that industry ought to be doing more in this area and fear we are being redundant. Yet industry cannot underwrite all research and development. Boards of big corporations will not and cannot accept too many long-term risks.

"Transfer," which comes from today's jargon of "technology transfer," means demonstrations, sometimes control activities, the showing that what works in the lab also works in the field and the testing of its applicability for the purposes of health. The last "T" of SATT is for training. In this graph about 5 percent of resources are for training. If we had used SATT in 1964, 25 percent of the total resources would have been in training. This training, incidentally, is all NRSA† training and does not include the more advanced and continuous development of scientists, the constant education that ends only when a scientist's career has finished.

In the debates on the 1980 budget, the Administration accepted the idea of trying to make our system a bit less subject to fluctuations in appropriations. They underwrote a first attempt on stabilization, for the present referring to the ability to underwrite a certain minimum number of new and competing ROIs and POIs each year.

* Research Career Development Award

† National Research Service Award

We adopted a figure of 5,000 new grants as an annual floor to be sought in the appropriations process. In 1979, we had 5,900 new starts; in 1978, 5,400; but before that fewer than 5,000. Such a proposition also left us with a total of about 16,500 active research project grants, about one-third of them being re-competed each year.

In the debates on the 1980, 1981, and 1982 budgets--even through the several proposed recissions--the struggle for stabilization was taken up by both Administration and Congress. Successive Secretaries helped us worry about our "5,000 grants." The President, in his budget, supported the concept, and the House and Senate appropriation committees agreed.

Inflation has put stress on the capacity to fund some other mechanisms in order to maintain the 5,000 new research grants. Over the past several years the research project grant line has risen from 46 percent to 50 percent, a relatively large change in such a large and complex budget. We may have reached the limit of desirable increase in funds for project grants compared with other important mechanisms of support.

Working as hard as you do through the peer review system to choose the best (and it is often a very difficult choice), you need to have an understanding of what this strategy is all about. I hope you also approve of it. Stabilization has become a watchword. It has been extremely important through recent budget periods in maintaining support of science by NIH.

The NIH will continue to examine itself. We will attempt, with your assistance and advice, to discover where we need further to shape the contours of resource allocation. I emphasize again that we can't worry only about project grants. An unbalanced system will tip over and cease to fulfill its promise and intent.

The outlook for public support of science, in my view, still looks good. These are not easy times, but you need not be despairing. In your study section roles you are the ones who have the keys to the future of biomedical research. If the method of quality control breaks down, then I think we will find very little public interest in the support of science. The whole thing rests on the continuance of the excellent performances that study sections and review groups have given since the beginning of this remarkable era.

Now, I would like to open this up to any questions you may have.

A. DISCUSSION

Question: If there are 5,000 new and competing renewals per year, it is possible that those new and competing grants could have twice the price tag of previous ones. With the new budget, is that feasible?

Dr. Fredrickson: No, it's not feasible. The great problem in trying to build any stabilization of research support is inflation. The cost of the average grant has increased annually over the last several years by more than 10 percent. If this continues unabated, it will be impossible for any Administration or any Congress to keep up with a stabilization design.

It is, I think, part of the miracle that we have managed to hold the 5,000 figure, in the face of such inflation. New monies have been added, but not enough to make up the difference; and some of the other mechanisms have had to decline. Thus we have to evaluate constantly the effects of shifting the support for research from one form to another.

Granted the great difference among scientists and the way they must effectively operate, we have to maintain our flexibility so that we do not lock ourselves into an impossible pattern. We must try to get a citizens' agreement about the minimum number of grants needed to keep this kind of inquiry alive and in good health.

Question: In developing the concept of stabilization, was any account taken for the continuing increase in the number of qualified principal investigators who will be competing for support?

Dr. Fredrickson: The full mastery of the dynamics of biomedical research, including the flux of investigators in and out of the system, eludes us. We have neither adequate information nor a completeness of controls; for absence is a plural process having both public and private components not amenable to complete reporting on any master plan. What keeps people still applying and sending in excellent grant applications when only about 30 percent of them are funded? What happens when training continues to decrease? There are many things going on in your institution now that you may not be aware of, and that we see only in a microscopic way. There are certain changes in the numbers and kinds of people who are applying for grants, the number of grants per scientist, and so forth. We perceive many useful trends; we have no precise equations to plot creative energy or human impulse.

This makes it very difficult for us to adjust our training needs. What, for example, would be the right number of trainees if we were reduced to 4,000 new research grants each year? Or to 3,000? Would we leave training efforts at the same level? Obviously we would like to have long-range predictions of the budget, but given the uncertainties of politics and economics, this is impossible.

Comment: Surely you must have some notion, even though a gross notion. With 5,000 as a base and a cutback in training, 5,000 investigators today will have quite a different attainability in terms of receiving research grants than the same number 5 or 10 years from now when the investigator pool size has presumably shrunk.

Dr. Fredrickson: I agree that we ought to be able to predict, but don't make too many rash assumptions. We don't know precisely how important NIH training is in controlling the flux of investigators into the system. We are probably training half of the people, at the most, who eventually come into the system.

It is interesting that the NIH support for training has been turning down for some time, but the number of new entrants into the field is not going down correspondingly. NIH training programs are not a perfect control on entry into biomedical research as a profession. They are more important for maintaining the overall quality of training than the supply.

Question: I would like to raise an issue that we touched on this morning. We are fairly confident of our ability to sort turkeys from eagles. The problem comes in distinguishing grants that are, by and large, all good. The NIH is now in the position where all these grants can no longer be paid. Are you putting any thought into how you decide exactly what to pay among these grants?

Dr. Fredrickson: This is a most important question, and I don't have a new idea to throw to you that you haven't already thought about yourselves. If ideas can be tested for some other way of making close distinctions, we will be very interested in assisting in such experiments. Program relevance will undoubtedly also become a more important factor than it ever was in the past. In the past, we turned the faucets on and the level of the water determined what grants we paid.

You want "program relevance" to interfere as little with your decisions as possible. So do I. But there will be more of such perturbation of the "merit system" in the future. You must not believe, however, that your decisions are being overturned capriciously. How much of this occurs will depend mainly on the budget. It cannot help but be a source of anxiety and burden for you. Still, you can only do what is humanly possible.

Question: If the NIH appropriations do not increase as fast as inflation in the coming years, will the medium size of a funded grant necessarily decrease during stabilization?

Dr. Fredrickson: No. If we don't keep up with inflation, and we probably won't, then 5,000 will be an undesirable, an unobtainable number. We will not reduce the costs of a grant to any level or sacrifice other essential services simply to maintain a number of 5,000.

Question: Do you mean the floor may change from year to year?

Dr. Fredrickson: We will keep our emphasis on research grants, but the number of grants that we might set out as our goal will have to be adjusted to the amount in our appropriation. The floor may change, if necessary.

Question: You aren't guaranteeing a baseline number of funded grants?

Dr. Fredrickson: You can't, unless you are in a state that guarantees to maintain your purchasing power against all pressures. What you gain by attempting stabilization is partly in making it easy for people who have little understanding of science, but who are still interested in it, to track the course of its support. I can't tell you how crucially important that could be in Washington, a town where each element in a complex mix gets only so much attention.

Comment: It seems to me that there will be a tendency, once you fixed on a number, to want to hold it. I think that is a desirable tendency, once you have decided on a number. But if that is the case and the inertia carries over into a subsequent budget year, then the best grants on an average will be paid less than the best grants of previous years.

Dr. Fredrickson: Many of us realize the difficulties you have and how tough you are on budgets. Obviously we cannot continuously shrink all of the grants in order to keep paying a certain number.

Question: When you sponsor research grants, why don't you just send the principal investigator a copy of the item-by-item analysis of what the institution is spending on indirect cost lines?

Dr. Fredrickson: Given the freeze on Federal employment, we would never have enough people to send you such information. It is more likely something the investigator should obtain from his institution.

We have had scientists, university administrators, auditors, and OMB types around this table not so long ago for frank talks about indirect costs. Your universities, many of them, are bearing more of the cost of research than they are being reimbursed, and I don't know that there is ever going to be any way we can reverse that situation. You may disagree with the way the institutions use their indirect costs. There may be some inequities, maybe even improprieties. We do not do the accounting of the indirect costs. They are done by regional auditors.

We might be coming closer to a day when we will have to put it all out on the table and negotiate one fixed price through bargaining between institutions and investigators.

Question: Are there any projections for the long-term dissolution of training funds and training programs?

Dr. Fredrickson: No. You can look at the trends for training and note that 10 years ago we had about 18,000 trainees; today we have 10,500. The number has been going down slowly but steadily over the years.

We're all certainly going to have to consider what relationship training should have to our capacity to fund new grants. What if, in a given year, the number is not 5,000 grants but 4,000? Should we then proportionally drop training?

In terms of research training the Administration has taken one view, and Congress has taken another. My guess is that we are not going to see training increased above the current level. Clearly, we are not going to go back to the days when 25 cents of the NIH dollar went to training. We were creating a system then; now we are trying to maintain it.

It is particularly hard to grapple with the philosophical issues of supporting graduate education in America. The other societies with which we compare ourselves are nearly all subsidizing technical education very heavily. Do you know anybody in France or Germany who pays \$15,000 a year to go to medical school? Yet we have strongly, and I think wisely, provided good government support for trainees in scientific research in America.

It is an extraordinary time. I call it the confrontation of the glorious and the dismal sciences. Never have the biological sciences offered more opportunity; seldom have economic constraints called for more selectivity.

FY 1982

February 18, 1981

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement by the Director

Mr. Chairman, I welcome the opportunity to appear before this Subcommittee to review with you the programs of the National Institutes of Health. I should like to begin with a brief overview of the organization, purposes, and activities of NIH before proceeding to a consideration of a few of the important issues facing this agency. For your convenience, I have provided a few charts and other information to which I shall refer in my presentation.

Introduction: Mission and Overview

The purposes of the National Institutes of Health are the conduct and support of biomedical and behavioral research, more broadly referred to today as the health sciences. The purpose of this research, in turn, is to prevent disease and premature death and assure each person born the maximum opportunity for freedom from pain and disability. Such research has had profound effects on mortality and life expectancy in the past 75 years. There are studies which support the conclusion that there is a very high return on the investment in health science in terms of controlling loss of productivity and income. Most assuredly, scientific research also holds the ultimate key to containment of the rising cost of health care.

In the last 25 years, the American contributions to the health sciences have been among the greatest in the world. It is generally conceded that knowledge of living things is increasing at an extraordinary rate. Biomedical technology has advanced very rapidly to a state which promises further important transformations in health practices, agriculture,* and industry. It is widely acknowledged, Mr. Chairman, that we are today experiencing a "revolution in biology."

This advent of a new age--comparable to the Space Age in which you had so noteworthy a role, Mr. Chairman--is the product of vigorous public support for scientific research in this country beginning right after World War II.

Since 1950 approximately \$75 billion, both public and private, has been spent on health science in the United States. The amount spent in 1980, about \$7.8 billion (chart 1), represents just over 0.3 percent of the Gross National Product and 3 percent of the annual cost of health estimated at around \$240 billion in 1980.

About 60 percent of the total support for the health sciences now comes from the Federal Government, with the next largest contribution coming from the pharmaceutical industry. An estimated 80 to 90 percent of the support for undifferentiated, fundamental or basic

* Recombinant DNA techniques may, for example, permit increased food production through the development of new disease-resistant plant strains.

research is underwritten by the Federal Government. One could not expect industry with its need to show profits in the short term to have ventured the large amounts of risk capital to support the basic science efforts over several decades which have led to gene recombination, the production of pure antibodies by fusion of a malignant cell with a lymphocyte (hybridomas), the tireless search and capture of the agents causing hepatitis, the remarkable discovery of slow viruses that cause brain degeneration, the elucidation of brain structure and function which explains the actions of lithium or other tranquilizers, to name but a tiny handful of modern discoveries. Even most of the current drugs used to cure cancer or to prolong the lives of cancer patients must be developed to a stage nearing profitability before their final development can be picked up by industry.

Of the \$7.8 billion estimated to be spent for biomedical research in 1980, half is represented by the budget of DHHS, with programs of 8 agencies contributing to the total. The budgets and activities of these agencies and how they interrelate in health research are described in a report, Health Research Activities of the Department of Health and Human Services, issued in December 1980 (copies of which have been provided to you). With its FY 1980 budget of \$3.4 billion, NIH supported approximately 85 percent of the Department's total research.

NIH was founded in 1930, but went through its most rapid phase of growth from 1955 to 1965. It has been the largest single supporter of biomedical research in the world for many years.

In 1948 NIH comprised four Institutes. Now it consists of 11, in addition to the National Library of Medicine and several research and support divisions. The organization of NIH is shown in chart 2, and the organization of a "typical" Institute in chart 3. FY 1980 obligations by Institute are presented in chart 4. About 80 percent of the resources of the Institutes are used to fund extramural research and training principally by grants to university scientists. NIH has been for some time the largest single source of R&D funds to American universities, especially the academic medical centers. All Institutes but one have intramural research programs. The largest concentration of these are located on a single reservation in Bethesda, where the Warren G. Magnuson Clinical Center, a 540-bed hospital, is integrated with more than a thousand laboratories. Intramural research is also conducted at other locations-- a 500-acre animal center at Poolesville, Md., a fundamental science laboratory at Frederick, Md., the Aging Institute's gerontology clinic in Baltimore, the National Institute of Environmental Health Sciences facility at Research Triangle Park, N.C., and the Rocky Mountain Laboratory for the study of infectious diseases at Hamilton, Montana.

Stabilizing the Science Base

A useful way to view the allocation of NIH resources in the aggregate is presented in chart 5. The left-hand cluster of bars represents dollar amounts allocated in FY 1981 for developing new

knowledge at more fundamental levels--identified as "Science Base" activities. Note that the bar on the extreme left, labeled "Research Project Grants," shows the total for the most traditional or "classic" mode of research support. Investigators submit research proposals, which are then examined intensively by experts under peer review procedures and are approved or disapproved. If approved, the application is given a priority score. The Institute's Advisory Council considers the proposals in light of biomedical and social needs. Taking into account these needs, the Council recommends funding as appropriate (chart 6).

Research grants are awarded for an average period of 3.5 years. Thus, in any year, the majority of grants are continuing commitments, which have first command on available resources. About one-third of previously supported grants compete each year for selection along with new grant proposals. In sum, the number of competing applications which can be funded in a given year represents the share of the excellent ideas which the Government can afford to support. The fluctuation of this number in past years has been a principal deterrent to those who would otherwise undergo the rigorous apprenticeship for research careers. It has also been our major focus for seeking some stabilization of the research enterprise in the face of austerity.

In our budget development, we have attached top priority to providing stable support for new and competing research project

grants. The effect of inflation on the costs of these grants is reflected in their actual average costs in 1979 and 1980 and projected costs in 1981 and 1982:

Average Cost per Competing Grant

<u>Fiscal Year</u>	<u>Amount</u>
1979	\$ 88,400
1980	98,700
1981	107,700
1982	116,500

Escalation of costs makes it extremely difficult to meet any specified target number of new grants. Although all the Institutes endorse the principle of stabilization of research project grant funding, some very difficult decisions have to be made regarding the other funding mechanisms. Inflationary pressures, combined with the priority given to the research project grants, tend to reduce flexibility in other research activities.

The categories identified in chart 4 to the right of Research Project Grants represent all types of activities essential in a continuum designed to move discoveries from fundamental research to practical applications.

Included in the activities contributing to the Science Base are categorical center grants, which integrate research with applications and provide multidisciplinary reach. Here are essential communal resources such as the National Library of Medicine's information systems, which provide service to the entire world. Here also

are the programs which supply the large instruments and data handling capability to many research institutions, the beds to permit clinical research, and other institutional resources. The largest single biomedical research center is the NIH's own intramural program. This year should see completion of the Ambulatory Care Research Facility, which adds a new dimension to multidisciplinary, ambulatory research.

The remaining 25 percent of NIH resources (those not in the Science Base) are critical for maintaining the continuity of research and its vitality. The largest component here is Applications Research, which includes development contracts to carry inventions into practice, and clinical trials to prove their safety and efficacy. A small, but necessary portion of NIH resources goes to technology transfer. Included here are demonstration and control activities to determine the practicality, safety, and efficacy of health practices. About four-fifths of the NLM budget is in this area. Finally, a small but critical 4 to 5 percent of our resources go to training and to the extended career development of especially promising scientists.

From its inception, NIH has supported the preparation of an important fraction of the Nation's biomedical researchers. Such research training support is now far less than in the time when the biomedical research system was growing. It is now in a pattern of replenishment to keep young minds and energies flowing into an

enterprise in which up to 10 percent of principal investigators are replaced each year.

The balance of all the elements in this biomedical research "continuum" is as important as the totality of resources in tempering any effects of fiscal stringency. Similarly, careful attention to the Government-university partnership which has always been the basis for the extraordinary productivity of American science is critical to keep this precious system vigorous and effective in times of austerity. I refer to the physical plants for research in universities as well as the faculty capabilities now maintained by and because of the essential link between scientific inquiry and effective teaching. Likewise, the need for accountability of use of public funds must be met short of excessive or unrealistic accounting; and finally, during the 1980s we will have to establish some clearer principles of cost-sharing between universities and the Government.

Another important matter requiring attention is the relationship of NIH research programs to industry, particularly in the areas of application and technology transfer. NIH will explore in some depth the question of royalty income from Federally held patents as part of a larger assessment of Government-private sector relationships at a forthcoming meeting of the public Advisory Committee to the Director.

Reallocations for support of biomedical science, in times when total resources are at zero-sum, or even shrinking, will not necessarily be done best by simple proportional changes in all distributions (by BID or by aggregate research activities). Care must be taken to see that: 1) selective growth is assured in the most productive areas of science and persistent activity in the most difficult areas in which need of knowledge is still great; 2) continued insistence is made upon excellence as a first guide to priority; 3) communal resources and stable funding for the most productive scientists are preserved; and 4) a well-balanced continuum from very fundamental to highly practical activities is retained.

Regulatory Activities

Finally, Mr. Chairman, I should like to address the Federal regulatory activities for which the NIH is responsible. I want to emphasize that the NIH has not had major regulatory responsibilities since the Bureau of Biologics was transferred to the Food and Drug Administration in 1972. This left the NIH with only a few specific and discrete regulatory activities.

Certain of these pertain to the award of research grants. Such regulations are issued by PHS or DHHS offices, although the NIH actively participates in their preparation. Compliance with this class of regulation is required as a prerequisite for receiving NIH research support. Of all the regulations that have bearing on the NIH program and activities, these involve the greatest amount of

time and attention from the private sector; however, the responsible and equitable distribution of NIH research grant awards could not be conducted without them.

The NIH tries to keep such requirements to a minimum and has recently simplified the standard research grant application form. A corresponding simplification of the progress reporting requirements for grantees is underway. Thus, the primary NIH involvement is the revision and simplification of forms and regulations. Costs associated with such activities are minimal.

A significant class of regulations are those which protect the rights and welfare of human and animal research subjects. Such regulations, first issued in 1974, are based on recommendations of the National Commission for the Protection of Human Subjects. The NIH's Office of Protection from Research Risks (OPRR) is responsible for developing and monitoring these; only minor revisions, however, are anticipated in the near future. OPRR is also responsible for educating the public on the implications of the regulations and for giving assistance and guidance to the scientific community as they take action to comply with the regulations.

Mr. Chairman, as you and the Committee members hear the testimony of the Directors of the Institutes, all of us will attempt to provide you the maximum of information you need in the extremely difficult decisions raised by the conjunction of economic constraints and unparalleled opportunities for advancing knowledge in the health sciences today.

NATIONAL COST OF HEALTH R&D, 1980

(IN MILLIONS OF DOLLARS)

Chart 1

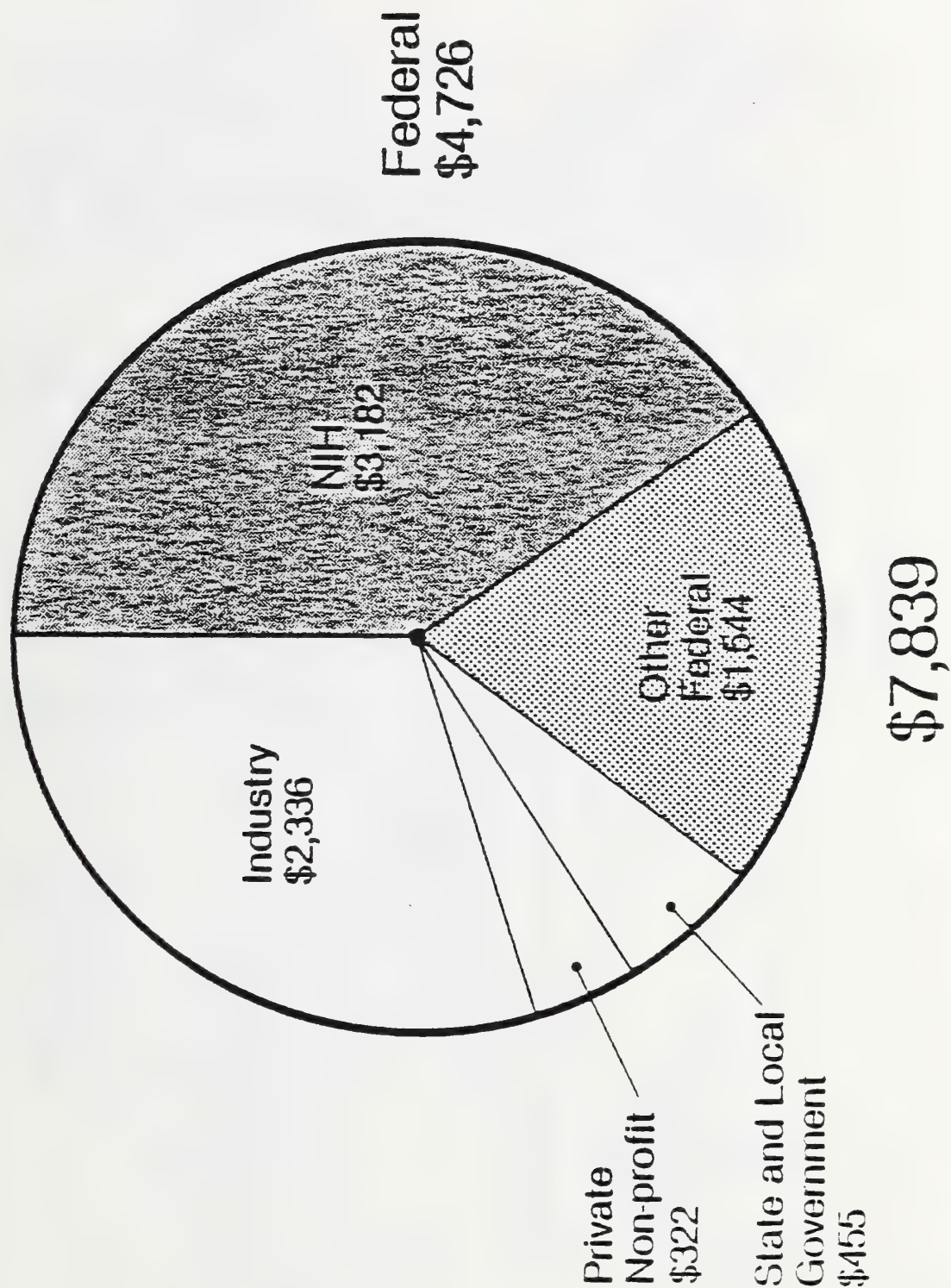


Chart 2

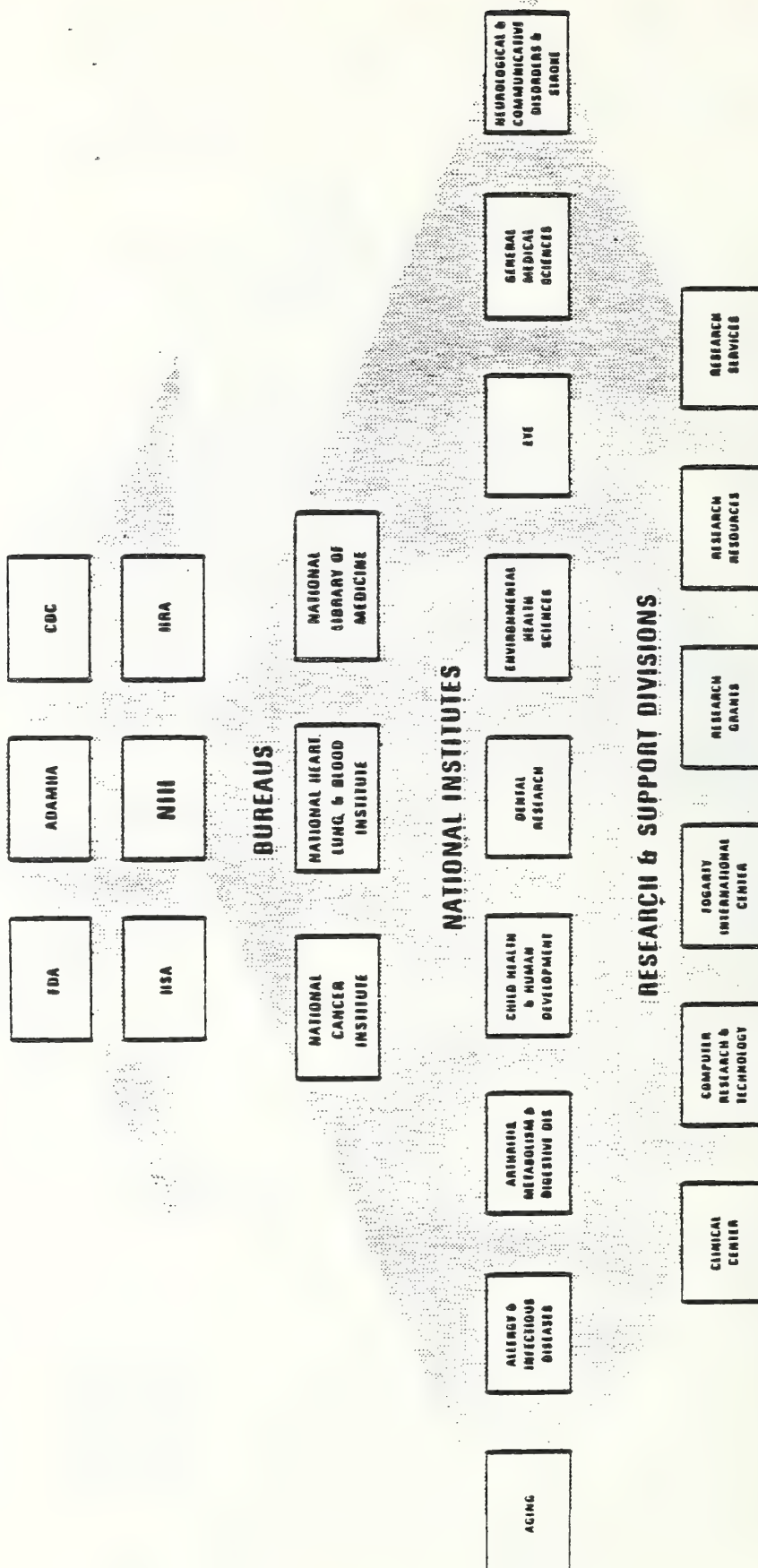
HHS**PUBLIC HEALTH SERVICE**

Chart 3

TYPICAL INSTITUTE OF NIH

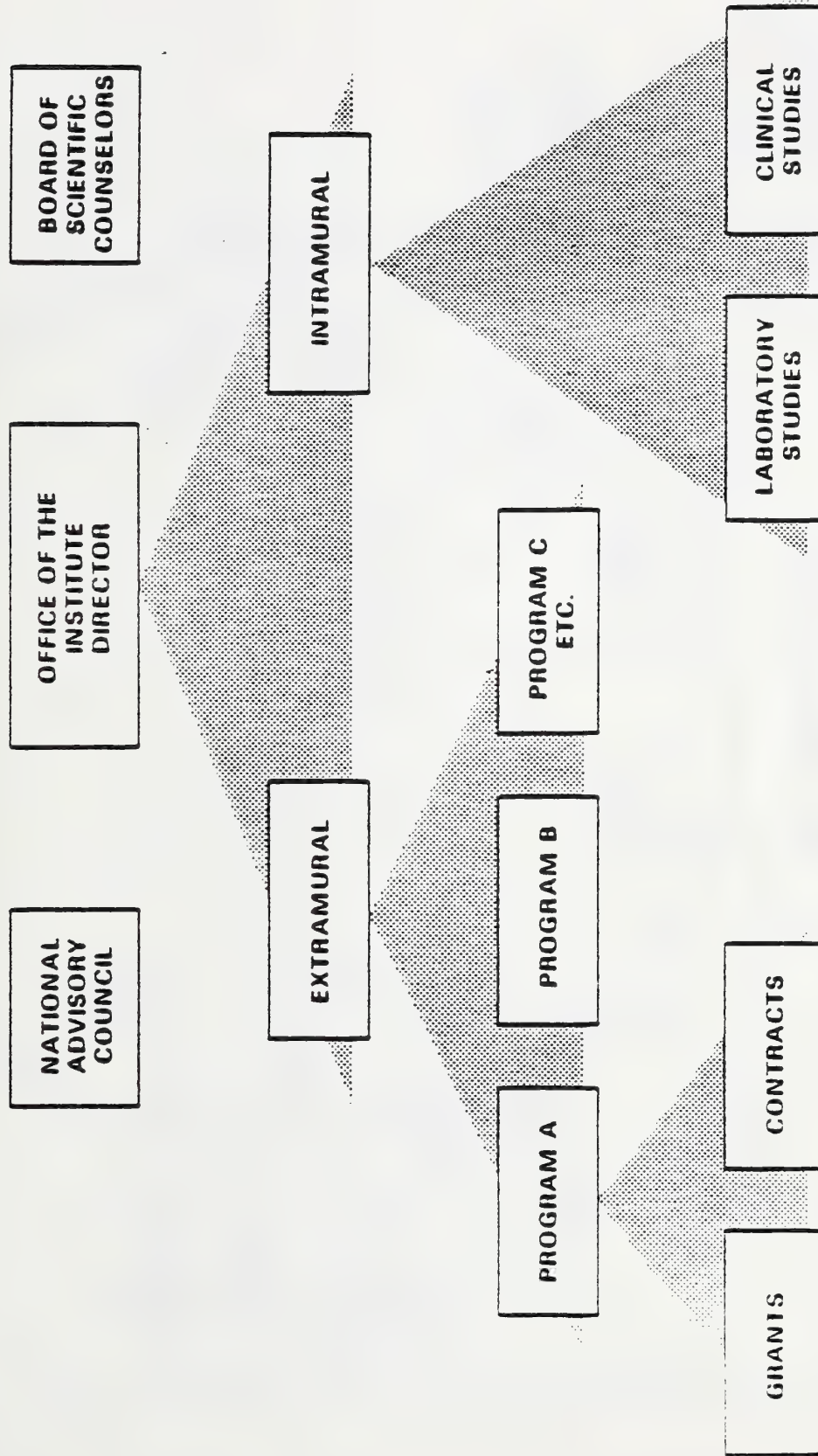
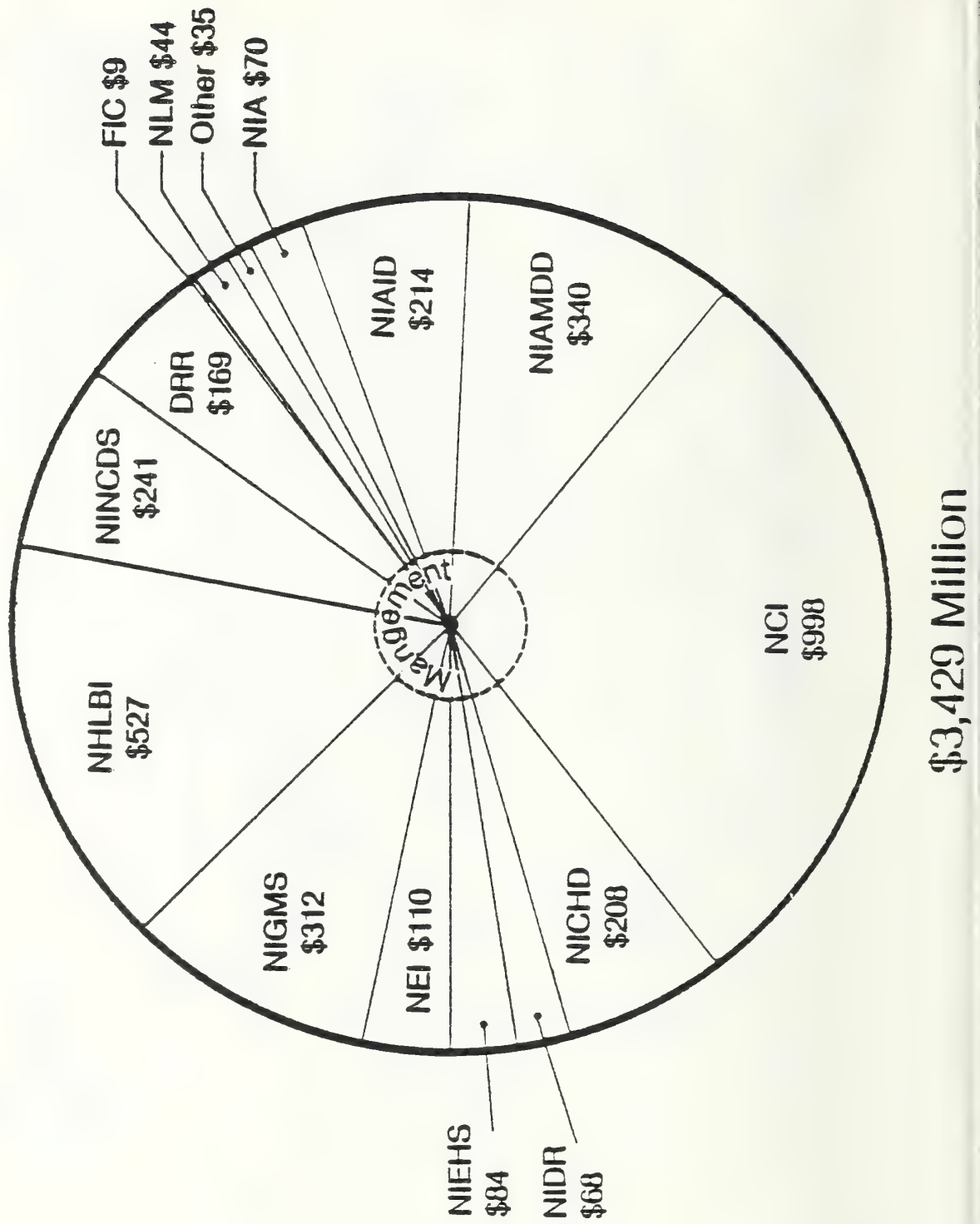


Chart 4

NIH OBLIGATIONS BY PROGRAM, FY 1980

(IN MILLIONS)



DISTRIBUTION OF NIH OBLIGATIONS, FY 1980

(IN MILLIONS)

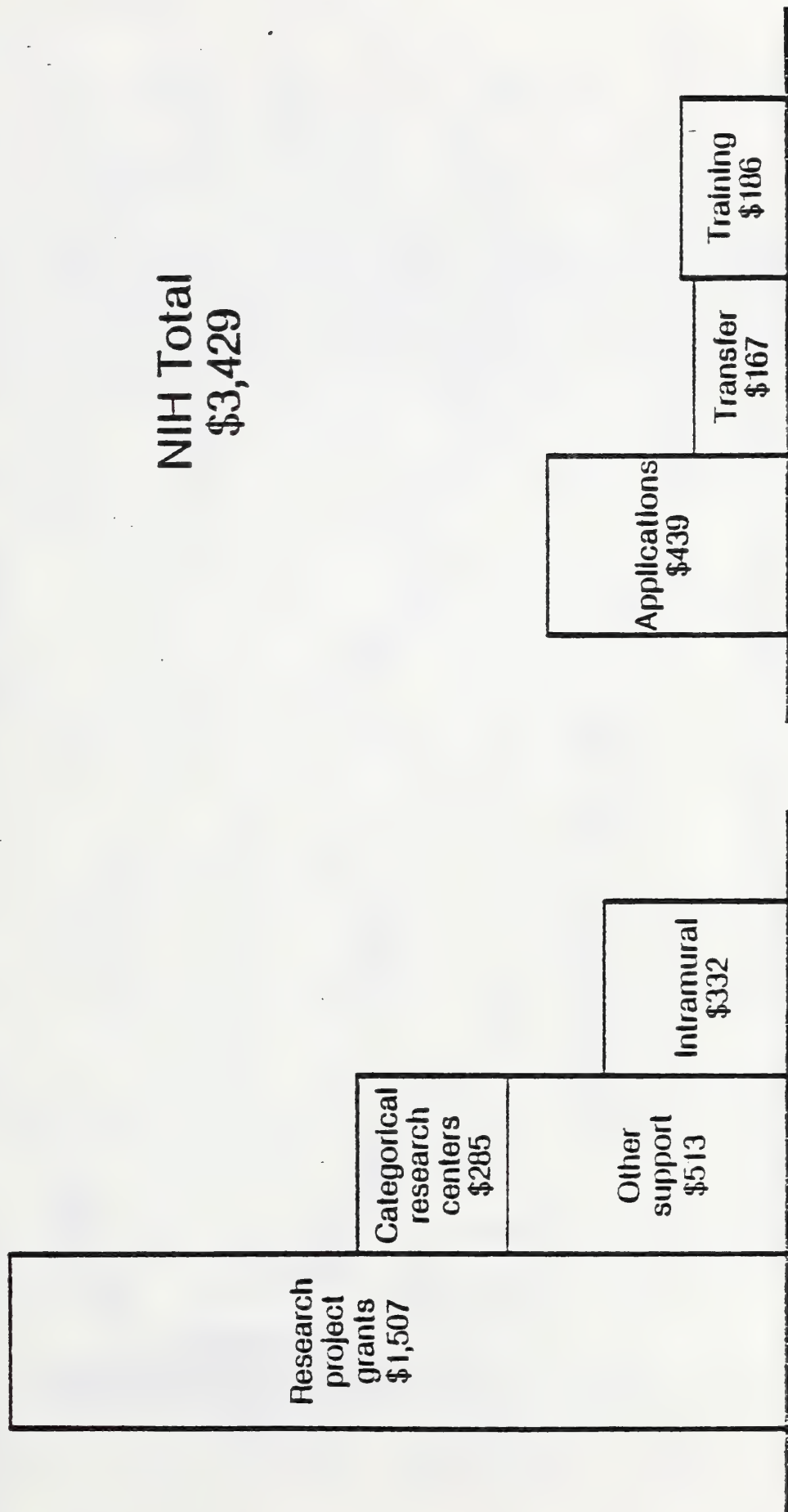
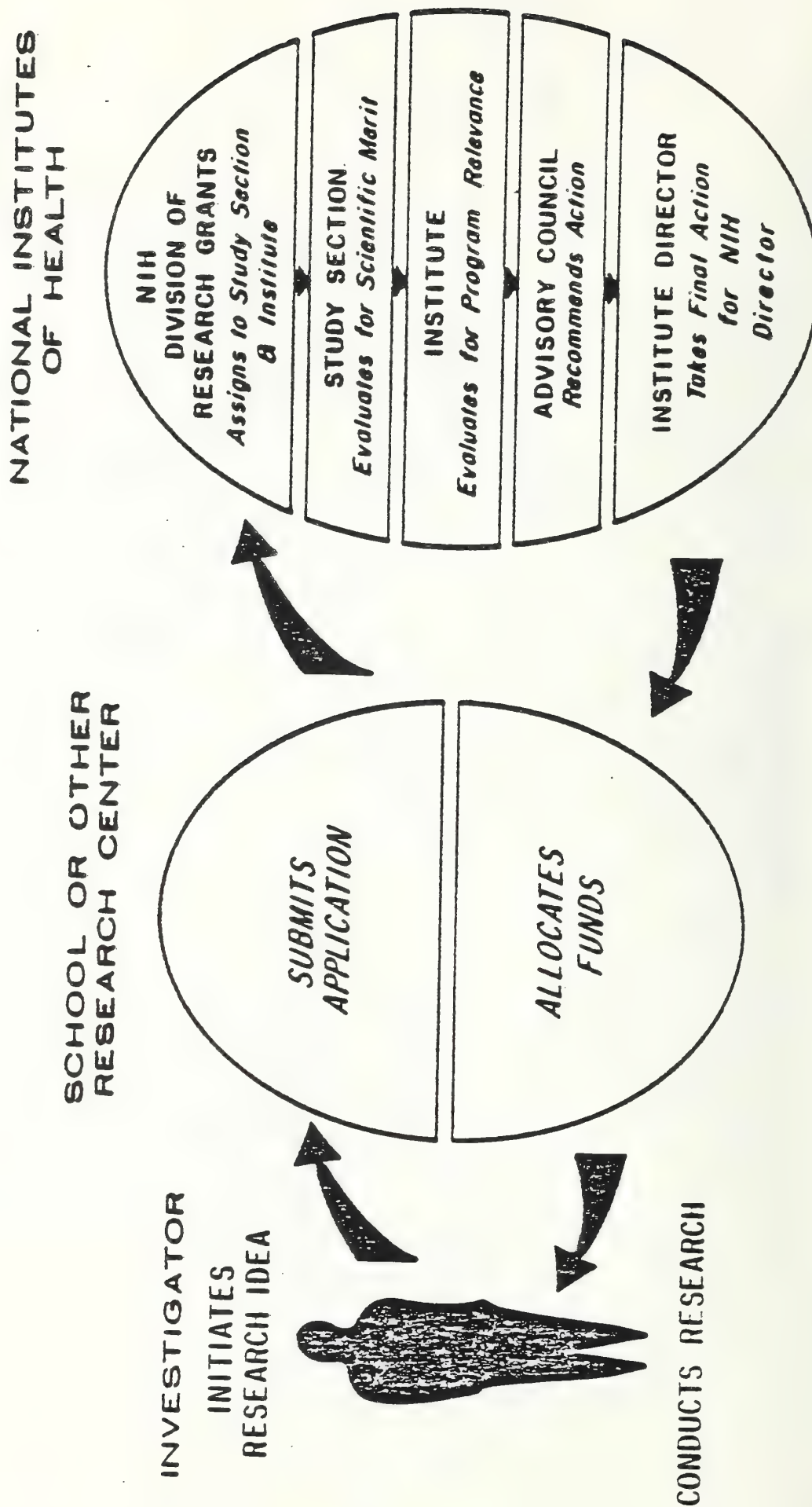


Chart 6

HOW A RESEARCH GRANT IS MADE



BIOMEDICAL RESEARCH AND PUBLIC PURPOSE*
(Synopsis)

Donald S. Fredrickson, M.D.**

René Dubos reminds us that we are uniquely favored among all creatures and thus doubly responsible. He puts us face to face with some harsh criticisms of biomedical research--that it is insensitive to human purposes and too narrow in its focus. Moreover, "If scientists expect a greater share of the public resources than other human activities, they must justify their claims by the ensuing benefits their work brings to society."

One approach to this timely question is to examine the system that has been created in America--mainly by the state--to foster and oversee biomedical research. Let us view both the impingements of the culture upon the science and its responses over a period of time, placing foremost Dubos' question whether science is interested in understanding only man's molecular nature or also the summation of his reactions to the cultural milieu.

From the beginning, public support of science through the federal government has had a strong practical bent. Consider the purposes of the land grant colleges (Morrill Act) and early national health organizations like the Army Medical Library, National Quarantine System, National Board of Health, and the National Hygienic Laboratory, which became the National Institutes of Health (NIH).

During World War II, government funds for biomedical research flowed toward immediately practical objectives through the Office of Scientific

*Presented at the "Saturday at the University" series, University of Pennsylvania, Philadelphia, Pa., on March 7, 1981.

**Director, National Institutes of Health, Bethesda, Maryland 20205.

Research and Development (OSRD). In 1945 Vannevar Bush, inspired by Franklin D. Roosevelt, recommended continued federal support of science. By 1948 the Congress had decided that the responsibility for biomedical research would be entrusted to NIH. In several decades of affluence and enthusiasm, this agency became the largest supporter and conductor of such research in the world.

The continued attention of the Congress, representing constituents who seek health, or relief from anxiety about it, provides a strong cultural warp upon which science weaves its way toward patterns of useful knowledge. At times the culture warp threatens to dominate or upset the "internal logic" of experimentation. A counterweight has been available from the beginning, however, in the form of the peer review system that provides quality control for NIH programs. All in all, a rather remarkable equilibrium has been maintained among the desires of the public, their political expression in the Congress, the institutions and people doing the research, and the increasing power of the scientific techniques themselves.

While freedom of ideas and basic research have been protected, medical research has always been mission-oriented through the division of activities by Institutes. Mission orientation has been modulated to adjust to need and opportunity. James A. Shannon, leader of NIH during its period of maximum growth, applied the term "saturation support" to the heavy concentration of high-quality basic-science projects initiated by individual scientists. This approach represents an effort to work at multiple points of the tapestry until patterns become visible and intervening gaps can be filled in by more rational design. The intense effort of three decades is now permitting large areas to be completed at an accelerating rate. Emphasis remains on investigator-initiated research, but need for development and clinical testing slowly increases.

More and more, synthesis succeeds analysis, and science proceeds toward mastery of some living systems. The most complex of these is man, and medicine is often the best tutor of the basic sciences. Its guiding influence assures a "humanistic biology," to use Dubos' term.

America has achieved a high level of clinical investigation. In designing the Clinical Center at NIH, Rolla Dyer and his colleagues created a Bauhaus for clinical research. With its 1,000 laboratories unified with 500 clinical beds, it was an institution as innovative as any at the time (completed in 1953) to combine the study of the "stuff and mechanics of life" with the "experience of life" (Dubos' phrases). The study of man in his milieu is a prime objective of the new Ambulatory Care Research Facility (ACRF) at the Clinical Center, scheduled to admit research patients at the end of the year.

Dramatic tugs on the culture warp of biomedical research occurred in the early 1970s with passage of the National Cancer Act, which some saw as threatening an irreparable tear in the biomedical continuum. Yet attempted cultural tilts to the scientific mechanism are modulated by the manner in which the Institutes are all expected and enabled to fund less-differentiated, more-basic research. Thus, the fundamental work of the Institutes is continuous and without boundaries.

There are pitfalls in the course of solving problems of large social import through scientific methods. Still, large-scale studies, like clinical trials, have progressed significantly in the last 20 years. Epidemiology and statistics have also proved to be reliable guides for orienting human biological research to culture and environment. All in all, I think we may reassure Rene' Dubos that biomedical research is moving in the direction toward which he has been pointing.

BIOMEDICAL RESEARCH AND PUBLIC PURPOSE*

by

Donald S. Fredrickson, M.D.**

Introduction

Réne Dubos had his eightieth birthday this month. Those Americans who were watching Public Television on a recent Friday evening had a chance to hear his conversation with Bill Moyers.

It was Réne Dubos, the "despairing optimist," reminding us, par lui-meme, that we are uniquely favored among all creatures and thus doubly responsible. It is a celebration-of-life to listen to this wise and gifted man, who is among the least parochial of researchers and the most scientifically trained of the humanists. Among scientists, Professor Dubos is one of few who truly merit the ancien titre Natural Philosopher.

This morning he has spoken of some philosophical matters that have concerned him progressively for many years. Productive scientists with a literary bent like Dr. Dubos trace a long horizon with their bibliographies. There, one can track the issues that have occupied their minds at various times. As medical microbiologist, Dubos' scientific works begin as early as 1927 in a paper with S. A. Waksman. During the thirties, he concentrated on bactericidal extracts from soil bacteria and related subjects,

*Presented at the University of Pennsylvania on March 7, 1981, in Philadelphia, Pennsylvania.

**Director, National Institutes of Health, Bethesda, Maryland.

including enzyme hydrolysis of pneumococcal capsules. The experiments helped Avery unwrap the important secret of DNA. Dubos' paradigmatic book on the bacterial cell appeared in the late forties. Articles on the tubercle bacillus now began to alternate with titles like "The Gold-Headed Cane in the Laboratory" and "The Philosopher's Search for Health." Pieces representing a transition in interests became increasingly more numerous. "Tulipomania" was such a hybrid, raising the mind-stopping question of whether there is such a thing as a "good" virus . . . or a "slow" virus.

Having contributed his share to the endless mosaic of new knowledge, Professor Dubos has now exercised his privilege of stepping back to speak from a wider perspective on how science expresses the nature of man and how well it serves human purposes.

In his more recent writings, Dubos puts us face to face with some harsh criticisms of research that challenge our consciences and behavior as scientists, individually and collectively.⁽¹⁾ We often meet Ortega y Gasset: "Science automatically converts the scientist into a modern barbarian." Or Mencken: "The prototype of the scientist is . . . but a dog sniffing tremendously at an infinite series of rat holes." Our escort also comments upon a progressive narrowing of the intellectual interests of scientists, which he thinks comes from "the widespread assumption that the discovery of new facts is the most important aspect of knowledge."

I should make it clear here that, to the extent that René Dubos is a critic of science, he is a critic of his own branch of

it, biomedical research. He values the biomedical sciences as "potentially the richest expression of science";⁽²⁾ and he obviously finds it intolerable for something he exalts to be so unaware of its shortcomings.

For many years Dubos has also been impatient with the degree to which the holistic in biology and medicine seems to be trammled by the reductionist. He deplores a common belief that the only fields of biology deserving to be called "fundamental" are those that deal with the simplest manifestations of life, and finds such a limited approach insufficient to create a science of life, let alone of man.⁽³⁾

Do not misinterpret the impatience of Dubos with the "one-variable simple system" prototypic of molecular biology. He has thought a great deal about the "internal logic" of science, and obviously he understands -- even ventures -- both its form and value for problem-solving. But he also urges us to be aware that "equally important is the external history of science. It is profoundly influenced by the social milieu and demands conversion into a form meaningful for society."⁽⁴⁾ He has admonished:

If scientists expect a greater share of the public resources than other human activities they must justify their claims by the ensuing benefits their work brings to society.

In the past six years, I have had an unusual exposure to the conjunction of the internal force and "external history" of biomedical science. The directorship of the National Institutes of Health is a helm from which one gains respect for both the

strength of the ship and the power and buoyancy of the sea that shape its course.

We are now in the midst of an incomparable period of growth in the knowledge of living things. If our ignorance remains vast, we are nevertheless on the threshold of important transformations in health practices, agriculture, and industry.

These achievements have reflected the commitment, beginning 30 years ago, of significant public support for research in the natural sciences. We are now in the midst of economic difficulties, and the people are going to have to make serious and difficult choices about the continued availability of federal funds for a variety of social programs. Modern biomedical research, especially its more fundamental aspects, is largely dependent upon the state. Thus it is a most important time for evaluating how well that research is organized and performing for the present and future benefit of its public patrons.

One approach is to examine the system which has been created -- mainly by the state -- to foster and oversee biomedical research and to view both the impingements of culture and the responses over a period of time. It is fair to place foremost Professor Dubos' question about whether science is interested in understanding only man's molecular nature or also the summation of his reactions to his cultural milieu. If I restrict my comments to American biomedical research and take a historical approach, I think you will be reassured on most counts.

The Emergence of Institutions

From the beginning, public support of science through the federal government has had a strong practical bent. The Morrill Act establishing the land grant colleges (1862) took an egalitarian and utilitarian view of improving the science of agriculture. Abraham Lincoln chartered the National Academy of Sciences (1863) to obtain better advice on weaponry. John Shaw Billings started a national medical library for the Army (1865). Established to fight yellow fever in the Mississippi Valley, a National Quarantine System (1878) and a National Board of Health (1879) provided the first national support for medical research. The first Public Health resources for research were in the National Hygienic Laboratory (1887), which moved from Staten Island to Washington in 1891.⁽⁶⁾

It took private philanthropy -- John D. Rockefeller, Sr.'s, money -- to establish the first institution devoted to basic biomedical research, the Rockefeller Institute, now University, in New York in 1901. This new climate of private endeavor may have stimulated the government in 1914 to designate beds for the study of pellagra at a U. S. Public Health Service hospital in Spartanburg, S. C.⁽⁷⁾ Two years earlier the Mann Bill had established the U. S. Public Health Service "to study and investigate the diseases of man and conditions influencing the propagation and spread thereof." It was easy to understand the tilt toward the infectious diseases in this charter.

In 1916 the National Research Council was created to stimulate a languishing National Academy of Sciences. Its Committee on Medicine became a locus for coordination of information about medical research activities. (8)

Science tends to make its quantum jumps through the distinctive contributions of relatively few people. This applies as much to the external or cultural forces acting upon the science as to the practitioners within. The accidents of timing or location perhaps play a heavier role on the cultural side. It is doubtful that Newton depended upon the fall of an apple from a particular tree. It is also likely that Lister would have had the same thoughts about antiseptics if he had been in Paris instead of Edinburgh. In the public support of science in America, however, it has mattered greatly who happened to be serving in the Congress at what particular times. As we celebrate now the achievements of the "new biology," it is important to see behind the 55 Nobel Laureates supported by the National Institutes of Health the shadows of some lawmakers and public figures who determined the pace if not the pinnacles that medical science attained in the last half-century.

One of the first was Senator Joseph E. Ransdell of Louisiana, whose service in the Congress began in 1898. (9) His more than 30 years there included unusual concern with public health. In 1926 Ransdell introduced a bill to create a National Institute of Health "to attack the fundamental diseases of man." The Bureau of the Budget opposed this \$5 million request, and it died. In 1928 the bill was revised, this time proposing that the Hygienic Laboratory

of the Public Health Service be renamed the "National Institute of Health" and that "fundamental" be deleted from the mission. The bill passed the Senate, but died in the House. In 1930, however, Ransdell saw his Act signed by President Herbert Hoover. When President Franklin Roosevelt dedicated the first buildings at Bethesda in 1938, Ransdell was 80 years old. He lived to be 96.

Senator M. M. Neely of West Virginia, beginning in 1927, annually introduced a bill to appropriate a \$5 million prize for the "discovery of a successful cure for cancer." Its failure to pass indicated that the legislature sensed the deficiency in this approach to a profound scientific problem. In 1937 Rep. Maury Maverick of Texas sponsored a successful bill to create a National Cancer Institute in the Public Health Service.⁽¹⁰⁾

Along with a \$400,000 appropriation, the Congress gave this new scientific institution a National Advisory Cancer Council, accompanied by a statement that "the endurance of our traditional form of government will depend in increasing measure upon the quality of expert judgment . . . available to government, and the willingness of government to follow such judgment."⁽¹¹⁾ Thus was articulated the principle of peer review in the dispensation of public monies for biomedical research. Review for both scientific quality and relevance to social needs was thought to be intended. And so remains the principle and practice today.

A loom had been set up for science to shuttle back and forth within a cultural warp, weaving patterns for the public benefit. The justice and good sense of this relationship have since been

amply demonstrated. It has taken time for the public side of that partnership to reach equal status. I wonder, though, what the bulk of the audience at the American Association for the Advancement of Science thought, back in the depression, when Henry Wallace declared that:

" . . . scientific research is a social process as much as business, political or religious activities are, and, as such, is interwoven with all other social processes, influencing them or being influenced by them." (12)

The European tradition, which still dominated science in those times, brooked no intrusion upon the laboratory of the professor: not the state, not the culture, not even the rest of the university.

During World War II, government monies for biomedical research in America flowed toward immediately practical objectives through the Office of Research and Development (OSRD) and the Committee of Medical Research. By 1944 it was evident that the war would eventually end and that America would become the most powerful country in the world, with concomitant responsibilities and opportunities to assume leadership in science.

Vannevar Bush was inspired by Franklin Roosevelt to make recommendations for federal support of science (1945). His "National Research Foundation" would have created a single funding agency, with one division for medical research. Stanhope Bayne-Jones urged the Congress to organize, coordinate, and support medical research on a national scale. Senator Kilgore introduced a bill to create a National Science Foundation that would have

been a high-level coordinator of all federal science support to universities. Medical scientists, however, favored the transfer of the war-time OSRD medical research contracts to NIH and the expansion of this complex to keep a unity of basic and applied research in biomedicine.

An unusual combination of events in this formative period has profoundly influenced the nature of biomedical research in the United States to this day. President Roosevelt died in April 1945. In July, both Bush's NRF and Kilgore's NSF proposals were introduced into the Congress. On August 6, however, the first atomic device was exploded over Japan. The Atomic Energy Act to assure husbandry of this prodigious and frightening offspring of atomic sciences quickly took center stage, and the other science proposals died in the 49th Congress.

On June 16, 1948, under the sponsorship of Senator Styles Bridges, new Institutes were added to NIH and its name was changed to the Institutes of Health. Having received the unfinished contracts of the wartime OSRD, NIH was destined to become the greatest supporter and conductor of biomedical research in America and, soon, in the world. Public Laws 80-655 and 80-755 added the National Microbiological, Heart, and Dental Institutes to the existing Cancer and Experimental Biology and Medicine Institutes.

In 1950 President Truman signed the bill creating the National Science Foundation. Its initial authorization was \$15 million.⁽¹³⁾ At the expanding NIH, the appropriation was already

\$52 million, and the principle of coordination of a continuum of biomedical research in a single agency had become ascendant. It would be an arrangement significantly different from that in most of the other countries of the world, where resources for the health and other life sciences have usually had separate guardians.

The Balancing of Forces

I have recently retold the story of the growth of NIH and summarized its role in the current "biological revolution." Here I want to concentrate on other aspects of that same remarkable period from 1950 to the present.

In contradistinction to views of a science heedless of social demands, I should say that greater weight has had to be exerted at times to prevent the cultural warp from dominating or upsetting the "internal logic" of experimentation. I would not rush to a judgment of imbalance, however. All in all, a rather remarkable equilibrium has been maintained among the desires of the public, their political expressions in the Congress and elsewhere in the government, the institutions and people doing the scientific research, and of course the increasing power of the scientific techniques themselves.

Indeed, some potential sources of tension have been avoided. As Pasteur demonstrated, and as others, like Weinberg, have more recently said, "In the biomedical sciences the distinction between pure and applied is rather irrelevant."⁽¹⁴⁾ The necessary

orthodoxy -- the rules of evidence in proof of a scientific hypothesis -- has to prevail at all times. Beginning with the creation of the National Cancer Institute, biomedical research has been highly mission-oriented at NIH through the very names and purposes of the Institutes.

The expression of mission orientation has been modulated by two principles. The first is that innovation arises in a scientific mold according to a dynamic of its own, determined by the techniques available for advancing the existing knowledge. The second is that the quality of the scientific hypothesis and methods proposed to test it will outweigh the immediate relevance of the question. Thus, very heavily in the beginning, there was an overwhelming emphasis on individual projects -- the pursuit of questions initiated by individual scientists -- competitively selected according to the quality of ideas and approach as judged by juries of their peers. James A. Shannon, leader of NIH during its period of maximum growth, termed the heavy concentration of such basic science "saturation" -- an effort to work at numerous points in the tapestry until patterns become visible and intervening areas can be filled in by more specific approaches.

With the intense effort that has been sustained over three decades, large spaces are now beginning to be filled in at an accelerating rate. Investigator-initiated research is still a dominant activity, but sustained development of promising innovations to quite practical ends is an ever-increasing reality. Intense reductionist activity has therefore unearthed numerous common denominators in biological structures and functions. More

and more, synthesis succeeds analysis, and we proceed toward mastery of some increasingly complex living systems.

Man is the most complex of these living systems. And medicine is often the best tutor of the basic sciences. Maintenance of proximity of human problems to the possibilities inherent in the techniques of science is one of the indispensable devices for assuring a humanistic biology -- to borrow another term from René Dubos.

Clinical Investigation

America has for some time achieved a higher level of clinical investigation than any other place in the world. Some say it was Rolla Dyer, Director of NIH from 1942 to 1950, who first had the idea of building the Clinical Center at Bethesda. Dr. Dyer was an outspoken advocate of federal support to non-government institutions, yet recognized the unique opportunities inherent in a collection of institutes covering all of biology in a single place.

In designing the unification of 500 clinical beds and 1000 laboratories in the Clinical Center, Dyer and his colleagues created a Bauhaus for clinical investigation. It was an institution as innovative as any attempt at the time to combine the study of the stuff and mechanics of life with the experience of life. I borrow the latter phrases from Dubos in his urging us to engage in "neo-Hippocratic science."⁽¹⁵⁾ The Rockefeller Institute complement of forty beds had been a much smaller model for the Clinical Center. There were also the Karolinska and the clinical research

units of Hopkins or University Hospital in London, or various research wards to be founded from 1940 on. The Pasteur Institute and the Kaiser-Wilhelm (now the Max Planck) had no bedside connection. And nobody had ever fashioned on this scale an institution to study both healthy and sick people, where the burdens of community medical care and the teaching of medical students were eliminated, where eager and curious young clinicians could move freely from clinic or bedside to laboratory, and where one had access to so many techniques and skilled tutors over so broad a spectrum.

Pulling on the Culture Warp

It will not suffice for the people desperate for discoveries to relieve a particular condition, or for the Congressional recipients of their anxieties, to be reassured that we are diligently pursuing with the general revenues a "humanistic biology" in their best interests. More reassurance is often demanded.

The interest taken by laymen in what scientists are accomplishing with public monies often runs deeper and takes numerous forms. I have time to mention only a few examples of how the Congress trims the cultural warp in biomedical research. There are the summing ups for particular "trans-NIH" problems. And influential efforts can change those ledgers lying athwart several sectors of biomedical research -- to assure our auditors that we are not neglecting any opportunities for discovery.

The nature of research and the unpredictability of its outcomes make allotment of expenditures to columns headed "nutrition," "population," or "behavioral" studies quite imprecise. Originally funds for recombinant DNA research could not easily be attributed to anything like "prevention." Now that the resulting technology may provide some of the most effective and safe vaccines ever imagined, we see easily the limits to such prior assessments.

Sometimes public impatience or frustration is transformed into legislative mandates for discovery or statutory banishment of ignorance. These can have many forms, and a few examples over recent years will illustrate the range.

During the last decade the Congress has involved itself to a considerable extent in the specific direction of biomedical research. Congressional interest, which is often reflected in the introduction of a bill, falls in several different categories. Congress has requested NIH to:

- Study the effects of a drug. H.R. 1718, introduced in the 97th Congress, directed the Arthritis Institute to determine whether DMSO is effective in treating arthritis.
- Examine the impact on the public health of toxic substances. In the 96th Congress, S. 2096 would have requested the Secretary of HHS to design and conduct an epidemiologic study on the effects of exposure to dioxins.*
- Increase support for specific categories of research. H.R. 4358, introduced in the 96th Congress, directed the Neurology

*Such a resolution actually passed as a rider on another bill. It was sent to the President with added language that a Congressional body, the Office of Technology Assessment, would approve the scientific protocol. In a Jeffersonian stroke for both science and the separation of powers, the President vetoed the bill.

Institute to double its budget for research on regeneration of the spinal cord.

In some instances, interest in both Houses of Congress leads to passage of a law. The 96th Congress passed P.L. 96-171, which directed NIH, in consultation with the Secretary of Transportation, to conduct a study on the effect of aging on the ability of individuals to perform the duties of airline pilots with the highest levels of safety and to decide from that study whether an age limit of 60 years is medically warranted.

A number of provisions of the Public Health Service Act reflect specific concerns on the part of Congress. For example, Public Law 96-622 (Sec. 301(b)(4)) requires the Secretary to publish, among other things, an annual report listing all known or presumed carcinogens to which there is a significant degree of public exposure. Public Law 95-623 (Sec. 309(g)) specifies that the Director of NIH, among others, shall provide an annual listing of health care technologies that are being developed and likely to be used. Similarly, Public Law 95-623 (Sec. 304(d)(1)) directs the Secretary, together with the National Academy of Sciences and a number of Federal agencies, to conduct a study of the present and projected future health costs of pollution and other environmental conditions resulting from human activity, to determine the contribution each pollutant makes to each disease, and to assess the effect of incremental reductions in pollutants on incidence or severity.

On occasion the Congress completely rewrites the law authorizing the mission and responsibilities of some of the Institutes.

In P.L. 92-423 the Congress redefined the authority of the Heart Institute by creating the National Heart, Lung, and Blood Institute. The Director, NHLBI, is to develop a plan for a National Heart, Blood Vessel, Lung, and Blood Diseases Program. The lengthening of the culture warp is visible in the authorizing language.

In addition to studies on diseases of the heart and lungs, the program shall give special emphasis to research on atherosclerosis, hypertension, thrombosis, and congenital abnormalities of the blood vessels as causes of stroke, and to effective coordination with related programs in the National Institute of Neurological and Communicative Disorders and Stroke. These and other activities of the NHLBI are to be included in a five-year plan, which is to be updated annually and transmitted to the Congress.

Occasionally administrative or organizational changes are introduced to shake up or redefine the particular kinds of knowledge being pursued. One example of such periodic evaluation is the nomenclatural refinement of what began as the Experimental Biology and Medicine Institute in 1947. This was renamed the National Institute of Arthritis and Metabolic Diseases in 1950, the National Institute of Arthritis, Metabolism, and Digestive Diseases in 1972, and the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases in 1980.

The power of determined citizens to obtain public resources for intensified scientific activity on a particular disease is not always reflected in the appropriations for a single Institute. An

example is the marked increase in research related to diseases like diabetes, which has effects on numerous organ systems that are the subject of work in many different laboratories. Much of this increase has been accomplished by several citizens' groups through various Congressional actions over a period of five to eight years. An extremely important disease, and one that has been peculiarly resistant to research for several decades, diabetes has merited this increased attention. It is already possible to credit important new knowledge to this emphasis. The next chart shows that diabetes research has expanded more rapidly than all NIH programs, having risen from about 0.5 percent to 4 percent.

The interaction of perceived significance of health problems, scientific opportunity, and Congressional interest is also reflected in the relative magnitude of research budgets over time. This is revealed by a percentage distribution of the Institute appropriations. Visible are the effects of dramatic tugs on the cultural warp of biomedical research which occurred in the early '70s upon passage of the National Cancer Act and the subsequent National Heart, Lung, and Blood Act. Some read the Cancer Act as threatening an irreparable tear in the biomedical "continuum." Several interesting histories of the times have been written.

Two major phenomena have prevented damage to the system from the intensity of cultural mandate-serving in biomedical research. One is an innate sensibility within the body politic to the limits of useful tampering with the scientific method. It emerges time and time again, sometimes in partisan repartee in the

Congressional hearing process, often in report language emerging from legislative conferences, and occasionally in Executive veto of rare excesses in law-making. From these activities, too, grow the necessary citizen capabilities to foster science wisely and to cope with the questions raised by its technological progeny.

There is another modulating influence on attempted cultural tilts to the scientific mechanism--at least in biomedical research. I call it the Venetian principle. It is inherent in the manner in which the Institutes, established with such definite categorical purposes and mission-orientation, are also enabled and expected to fund less-differentiated, more-basic research. Thus, at their foundations, the fundamental work of the Institutes is continuous, without boundaries.

Some, skeptical of my excessive bent for metaphor, have reminded me that Venice is sinking. I retort that, on the contrary, the water -- the great miscible body of knowledge -- is rising.

Biomedical Research Tomorrow

One of the less joyful aspects of responsibility for public institutions is the necessary assumption that if something is working right and having considerable success, we must always be preparing for change tomorrow. Given the speed of innovation today, and the accelerated demand for wisdom, it is inevitable and desirable that biomedical research will be steadily transformed. It will move in the direction of continuing synthesis of the mole-

cular with the experiential, on an ever larger scale, for the purpose of removing obstacles to the realization of human potential.

During the decade ahead, the fragile border between the social and the natural sciences must be tended carefully, so that what is now a nervous buffer zone will steadily be converted to a single stable community. New techniques, which will be primarily but not exclusively statistical ones, will increasingly provide opportunity for experiments integrating the disparate sciences.

The pitfalls in the course of finding solutions to many problems of large social significance through scientific methods are great. Some have interpreted as "snobbery" a great reluctance on the part of some biomedical scientists to engage in any human research. It is, in fact, a fear either of brushing against subjective values or of being so overwhelmed by the complexities that they will unwittingly commit a violation of the internal ethic (the rules of evidence) of science. Still, we have made significant progress in mission-oriented health science in the last 20 years. Consider large-scale clinical trials. We now have the ability to calculate the odds on cardiovascular events and thus permit the design of productive randomized clinical trials involving thousands of subjects and millions of dollars over periods of 10 or more years. This expertise was derived from a 25-year clinical study in Framingham, Massachusetts -- a costly project whose renewals were sometimes viewed with boredom, even dark suspicion, by laboratory scientists among the Institutes' administrators and advisors.

Epidemiology and statistics are the connection between culture and much of human biology. The geographic "cancer maps" and the time courses of mortality have opened numerous agendas for planning and setting of priorities in cancer research.

For some years, René Dubos has foreseen changes in present research institutions away from "highly individualized" (project) structure to "highly organized long range programs" or even a "collective form of intellectual life . . . akin to medieval monastic orders."⁽¹⁶⁾ Less insular and more exciting solutions for the problems created by civilization are possible. One is rising again in Bethesda.

As part of a modernization of the already mentioned Clinical Center -- quite recently renamed by the Senate the Warren G. Magnuson Clinical Center -- a new Bauhaus is under construction. It is an Ambulatory Care Research Facility (ACRF) joined to the older building. It contains no beds, but rather outpatient clinics and clinical laboratories in a setting designed to remove the sense of alienation often emerging from a hospital encounter. The ACRF symbolizes the increasing emphasis on prevention and ambulatory health care. It deemphasizes the intensive study of the in-patient to the extensive observation of people left in full contact with their usual physical and cultural environments.

What I dream this will mean, too, is a rise of multidisciplinary clinics in which the behavioral, anthropological, and other social sciences can be more completely integrated with the biological sciences and the medical, dental, and nursing professions in

study of complex disorders. What we must hope to create here are newer paradigms for understanding of the "dyslexias" and other disorders of learning; of minimal disabilities in communication which impair social adaptation; of behavioral and affective abnormalities having both intrinsic and extrinsic determinants; of the nature of dependence upon tobacco and similar other destructive habits; and of many other problems of people for which creative application of the methods from several disciplines can combine to achieve insight and relief that purely molecular views may not.

No Bauhaus sets new styles or alters the condition of humanity by mere dedication of money, equipment, or space. It has always depended, and will ever continue to depend, upon people. This is to say, upon people with the right combinations of disciplined intellect, sharpened curiosity, stubborn perseverance, and the human interest necessary for validating and extending discoveries until they produce lasting benefit to mankind. From astute selection and careful nurturing -- and with appropriate good luck -- the people who will catalyze the movements toward the profound new insights always eventually appear. Some, through individual performances -- as did Pasteur -- will leave whole institutes behind them. Some -- like Dyer -- will be the gifted impresarios who orchestrate star performers and supporting casts into brilliant, long-running productions. Biomedical researchers seek to catch the reflections of their own nature in the subjects of their observations. The views are nearly infinite, and integration of the whole will take much time. We may reassure René Dubos, however, that we are moving in the direction toward which

he has been pointing for some time.

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REMARKS*

by

Donald S. Fredrickson, M.D.**

Thank you, Bob Gordon. You've added again to the many comments about the skill that James Shannon had in picking people. Such comments usually come from those who were picked by him. They include yourself.

I'm very pleased to accept this photograph of Jerome Cornfield. I will see that it is suitably framed, given a brass plate, and hung among those who will remember his gifts. Indeed, I came into this meeting just in time to hear Sam Greenhouse refer to "miraculous qualities" and I see the beatification of Jerry Cornfield has appropriately begun. I understand the celebrants here actually had their symposium last night. (Symposium is a Greek word for drinking party.) Today is an appropriate, more formal opportunity to comment upon an extraordinary man and a good friend of a great many of us.

The last time I saw Jerome Cornfield was in this room in 1978 when, as Director, I presented him with an NIH Director's Award. I had known Jerry much earlier, however, because I was the Director of the Heart Institute in his last year here. It was to me that he told the unbelievable news that he was going to leave NIH, and it was I who had the impossible task of trying to replace him.

I'd like to make a nonparametric assessment of Jerry Cornfield. You've heard Sam describe what he did scientifically, and I'm sure others of you who are experts in his area will do the same. To me, Cornfield was someone between the Willard Gibbs and the Willy

* Presentation of photograph on the occasion of "Current Topics in Biostatistics and Epidemiology: A Memorial Symposium in Honor of Jerome Cornfield." Masur Auditorium, March 9, 1981.

** Director, National Institutes of Health, Bethesda, Maryland.

Sutton of Clinical Trial Mathematics. With only a bachelor's degree, yet a peer of the doctorates, he represented a mockery of excessive adherence to traditional qualifications. Among the Cornfield achievements that I best understood was his great enhancement of clinical trials in cardiovascular disease by adjusting the prediction of cardiovascular events to the precision of a well-run casino. I remember particularly how he and his successor, Max Halperin, helped me prepare a footnote to a paper I once gave, which described alpha and beta to an audience of amateurs -- including the speaker. Sometimes I like to go back and just read that footnote to remember again how clearly Cornfield could see the simple things and how he knew unerringly "where the money was" in the world of field trials. As you've perceived and as I hear in the remarks that have been made, there was also some greater quality to Jerry Cornfield, some mysterious depths of wisdom, waiting to test those who could plumb them. All institutions depend upon people. Surely the kind of institutions that we all represent depend especially on certain human qualities. Jerry Cornfield had them in rare abundance. This symposium does us all honor in providing the opportunity to remember such a remarkable man. I am glad that I have this opportunity to say these things on behalf of all NIH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement by the Director

Mr. Chairman, it is a pleasure for me to be here today to review with the Subcommittee the 1982 budget request for the National Institutes of Health. For the benefit of new Subcommittee members I should like to begin with a brief overview of the organization, purposes, and activities of NIH before proceeding to a consideration of a few of the important issues facing this agency.

Introduction: Mission and Overview

As you know, the mission of the NIH is the conduct and support of health science research. The purpose of this research, in turn, is to prevent disease and premature death and assure each person born the maximum opportunity for a productive life free from disability. Such research has had profound effects on mortality and life expectancy in the past 75 years.

In the last 25 years, the American contributions to the health sciences have been among the greatest in the world. Our knowledge of living things is increasing at an extraordinary rate, with biomedical technology advancing to a state that promises further important transformations in health practice, agriculture, and industry. It is widely acknowledged, Mr. Chairman, that we are today experiencing a "revolution in biology."

This advent of a new age is mainly the product of vigorous public support for the health sciences. About 60 percent of the total support for the health sciences now comes from the Federal Government--with the next largest contribution coming from the pharmaceutical industry (chart 1). An estimated 80 to 90 percent of the support for undifferentiated, fundamental or basic research is underwritten by the Federal Government.

Chart 2 shows national support for health R&D by source and by performers. It may be seen that 38 percent of the R&D is performed by universities and 29 percent by industry. The Federal Government, by far the largest supplier of funds, itself performs only 16 percent of national health R&D. The universities, where most of the basic health research is performed, receive only 3 percent of their support for this purpose from industry and nearly 80 percent from NIH. One could not expect industry with its need to show profits in the short term to have ventured the large amounts of risk capital to support the basic science efforts over several decades which have led to gene recombination, the production of pure antibodies by fusion of a malignant cell with a lymphocyte (hybridomas), the tireless search and capture of the agents causing hepatitis, the remarkable discovery of slow viruses that cause brain degeneration, the elucidation of brain structure and function which explains the actions of lithium of other tranquilizers--to name but a tiny handful of modern discoveries. Even most of the current drugs used to cure cancer or to prolong the lives of cancer patients must be developed to a stage nearing profitability before their final development can be picked up by industry.

As you know, Mr. Chairman, NIH has for many years been the largest single supporter of biomedical research in the world. It now comprises 11 Institutes, in addition to the National Library of Medicine and several research and support divisions.

A total of \$3.762 billion has been requested for the NIH in 1982. The distribution, by Institute, is presented in chart 3. About 80 percent of the resources of the Institutes are used to fund extramural research and training principally by grants to university scientists. The NIH intramural programs are concentrated primarily on a single reservation in Bethesda, where the Warren G. Magnuson Clinical Center, a 540-bed hospital, is integrated with more than 1,000 laboratories. Intramural research is also conducted at other locations--a 500-acre animal center at Poolesville, Maryland, a fundamental science laboratory at Frederick, Maryland, the Aging Institute's gerontology research clinic in Baltimore, the Institute of Environmental Health Sciences facility at Research Triangle Park, North Carolina, and the Rocky Mountain Laboratory for the study of infectious diseases at Hamilton, Montana.

Stabilizing the Science Base

The main challenge facing NIH today is to sustain the capacity and effectiveness of the national biomedical research enterprise through a period characterized by high inflation, a concerted effort to limit or reduce Federal spending, a major reassessment of national priorities, and, at the same time, exceptional scientific opportunities in biomedicine.

The key element in current NIH program strategy is to assure an adequate and predictable level of support for investigator-initiated research project grants. This, if accomplished, would "stabilize" the single largest and most important component of the "science base," which in turn represents over three-quarters of total NIH programs (chart 4).

The principal source of new knowledge is research that is initiated and directed by individual laboratory and clinical investigators--hence, the priority of investigator-initiated research. Broad fluctuations in the number of research project grants that can be supported from year to year add an element of uncertainty that reduces the attractiveness of research careers for those who might otherwise be interested, and increases chances that good ideas may go unsupported if application is made during the down-side of the fluctuation.

In the past two years NIH has sought sufficient funds to support annually about 5,000 competing (new and renewal) research project grants. This number is based on the fact that NIH has been supporting about 16,000 grants annually, with roughly two-thirds of these non-competing continuations out of available resources. In accordance with this initiative, for FY 1982, approximately 4,900 competing research project grants will be supported, compared with 4,800 in 1981, 4,785 in 1980, and 5,944 in 1979.

Mr. Chairman, your Committee has reviewed and found merit in this "stabilization" strategy. However, the rising cost of individual research project grants has increased the proportion of NIH resources needed for this purpose and forced reductions in some other program areas, notably research training and research and development contracts. NIH continues to identify stabilization as its first budget priority, but recognizes that the imperatives of program balance must also be considered in determining the support levels for investigator-initiated research.

Support for Competing Research Project Grants

<u>Fiscal Year</u>	<u>Number of Competing Grants</u>	<u>Average Cost Per Competing Grant</u>	<u>Percent of Research Project Grants to All NIH Funds</u>
1979	5,944	\$ 88,400	44%
1980	4,785	98,700	46
1981	4,800	107,800	50
1982	4,900	116,700	50

In addition to research project grants, support for the science base includes categorical center grants, which integrate research with applications and provide multidisciplinary reach. Also included are essential communal resources such as the National Library of Medicine information systems, which provide service to the entire world. Here, too, are the programs that supply the large instruments and data handling capability to many research institutions; the beds to permit clinical research; and other institutional resources.

The largest single biomedical research center is the NIH's own intramural program, another element in the science base. This year should see the completion of the Ambulatory Care Research Facility, which adds a new dimension to the multidisciplinary, ambulatory research. I am pleased that the budget includes \$6.73 million to support the fourth year of the Clinical Center Modernization Program, a multi-year effort begun in 1979 to integrate the Clinical Center with the new ACRF and to correct functional obsolescence and physical deterioration in the parent hospital.

The remaining fourth of NIH resources are critical for maintaining the continuity of research and its vitality. The largest component here is applications research, which includes development contracts to carry inventions into practice, and clinical trials to prove their safety and efficacy. A small but key amount of NIH resources goes toward technology transfer. Included here are demonstration and control activities to determine the practicality, safety, and efficacy of health practices, and four-fifths of the NLM budget is in this area.

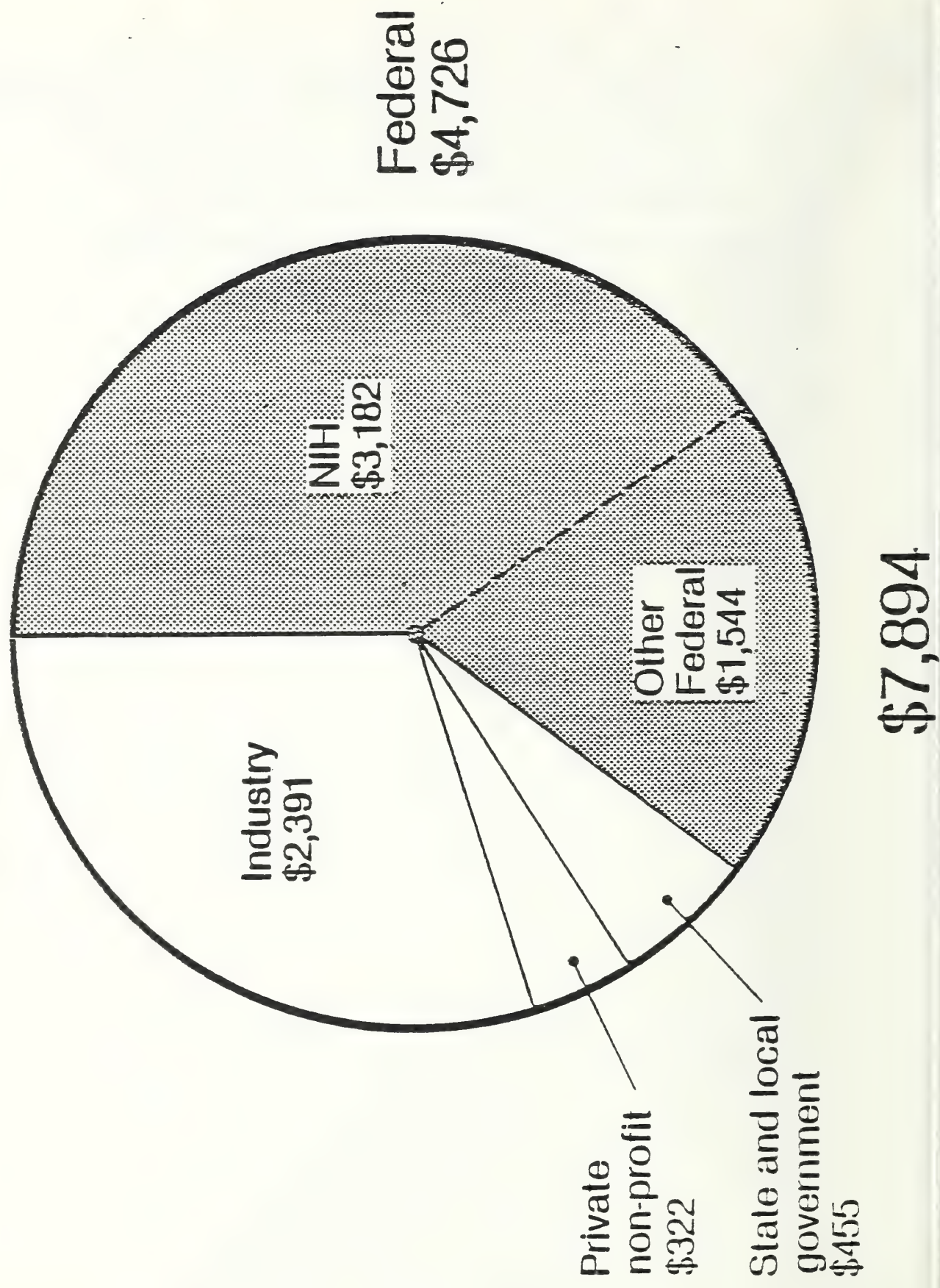
The last bar shown in the distribution of NIH resources in chart 4 is research training. For the period 1980 to 1982 the number of trainees maintained by NIH training grants and fellowships is approximately 10,000 each year. In spite of this level of support, the steadily dwindling supply of physician investigators is our primary concern, as physicians wish to go into private practice where the monetary rewards are greater.

Mr. Chairman, as you and the Committee members hear the testimony of the Directors of the Institutes, all of us will attempt to provide the maximum of information you will need in the decisions you must make concerning the allocation of public resources.

NATIONAL COST OF HEALTH R&D, 1980

(IN MILLIONS OF DOLLARS)

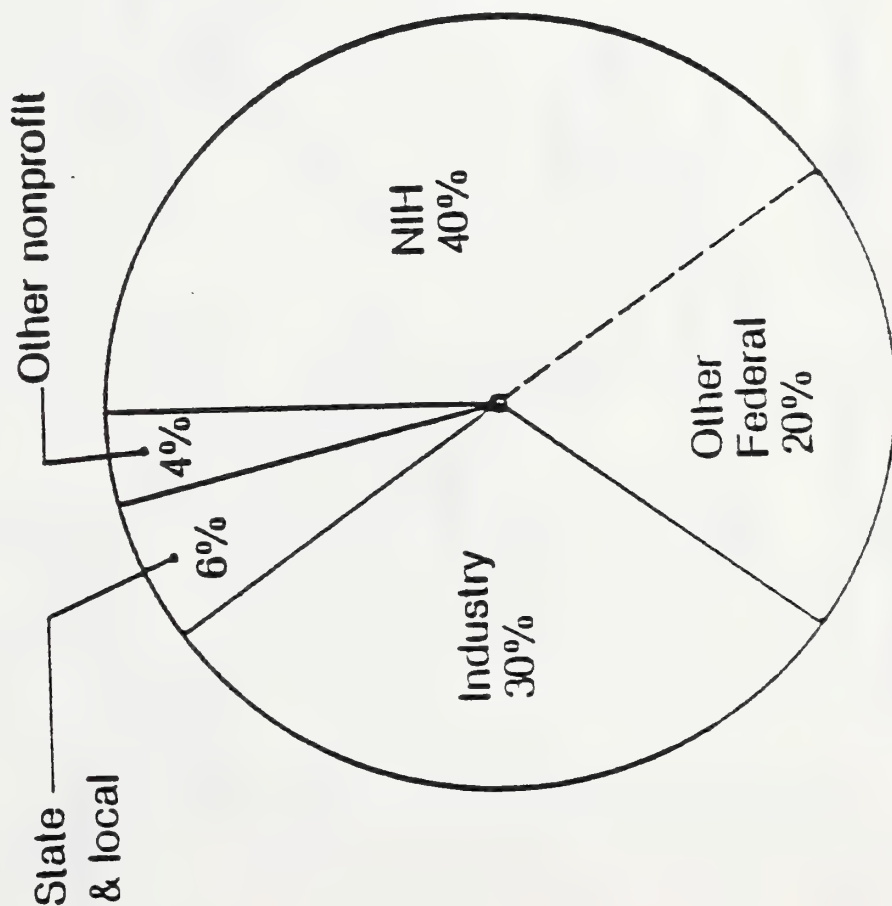
CHART 1



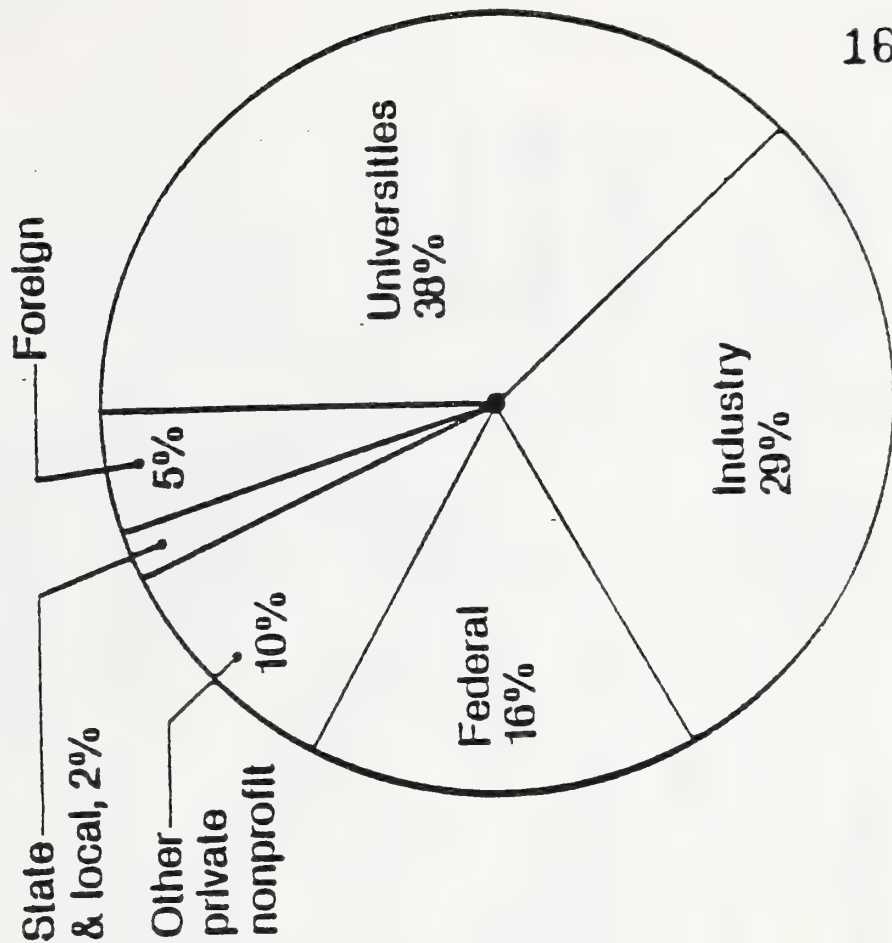
NATIONAL SUPPORT FOR HEALTH R&D, 1980

TOTAL — \$7.9 BILLION

BY SOURCE OF FUNDS

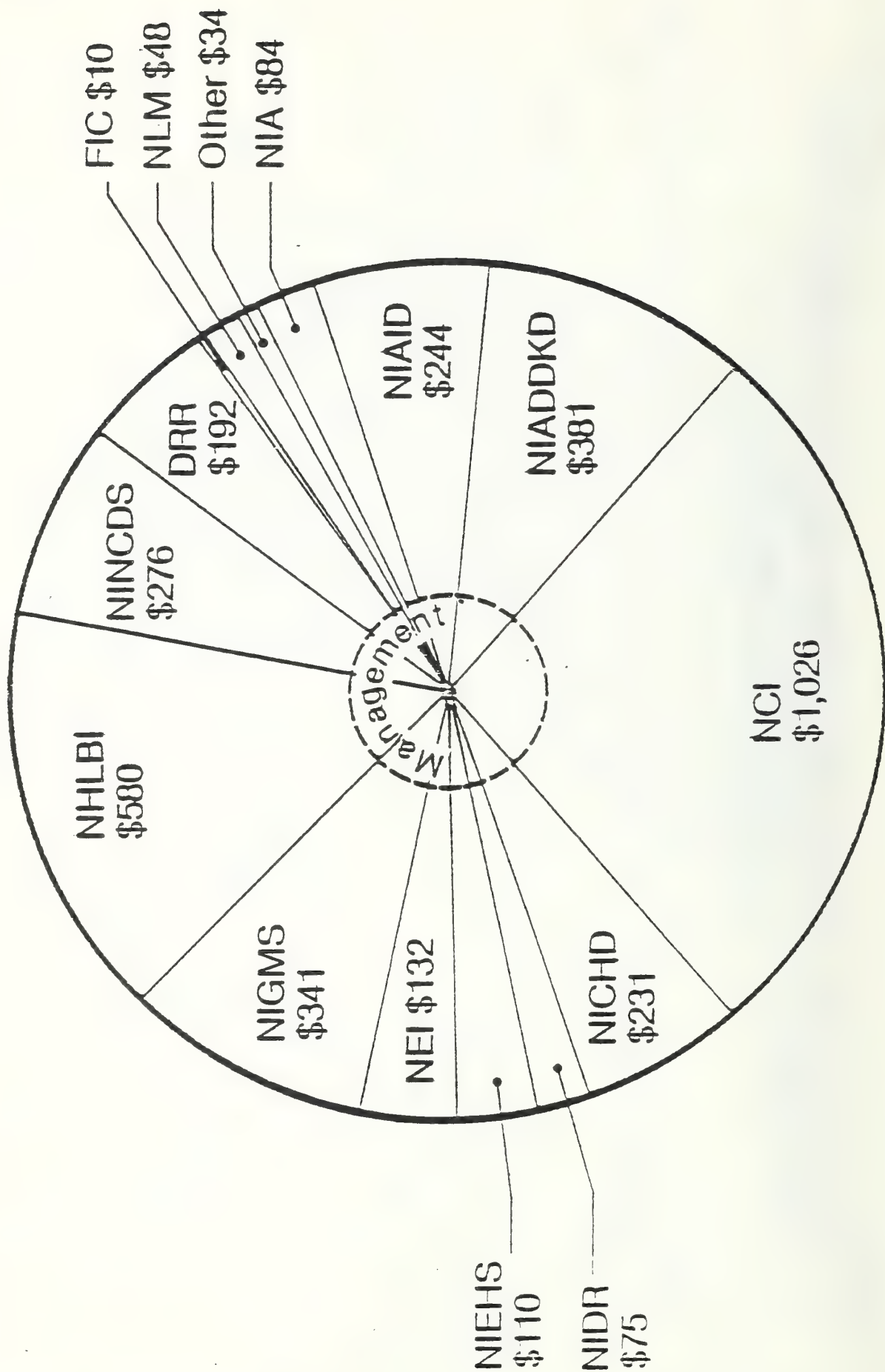


BY PERFORMER OF R&D



NIH BUDGET BY PROGRAM, FY 1982

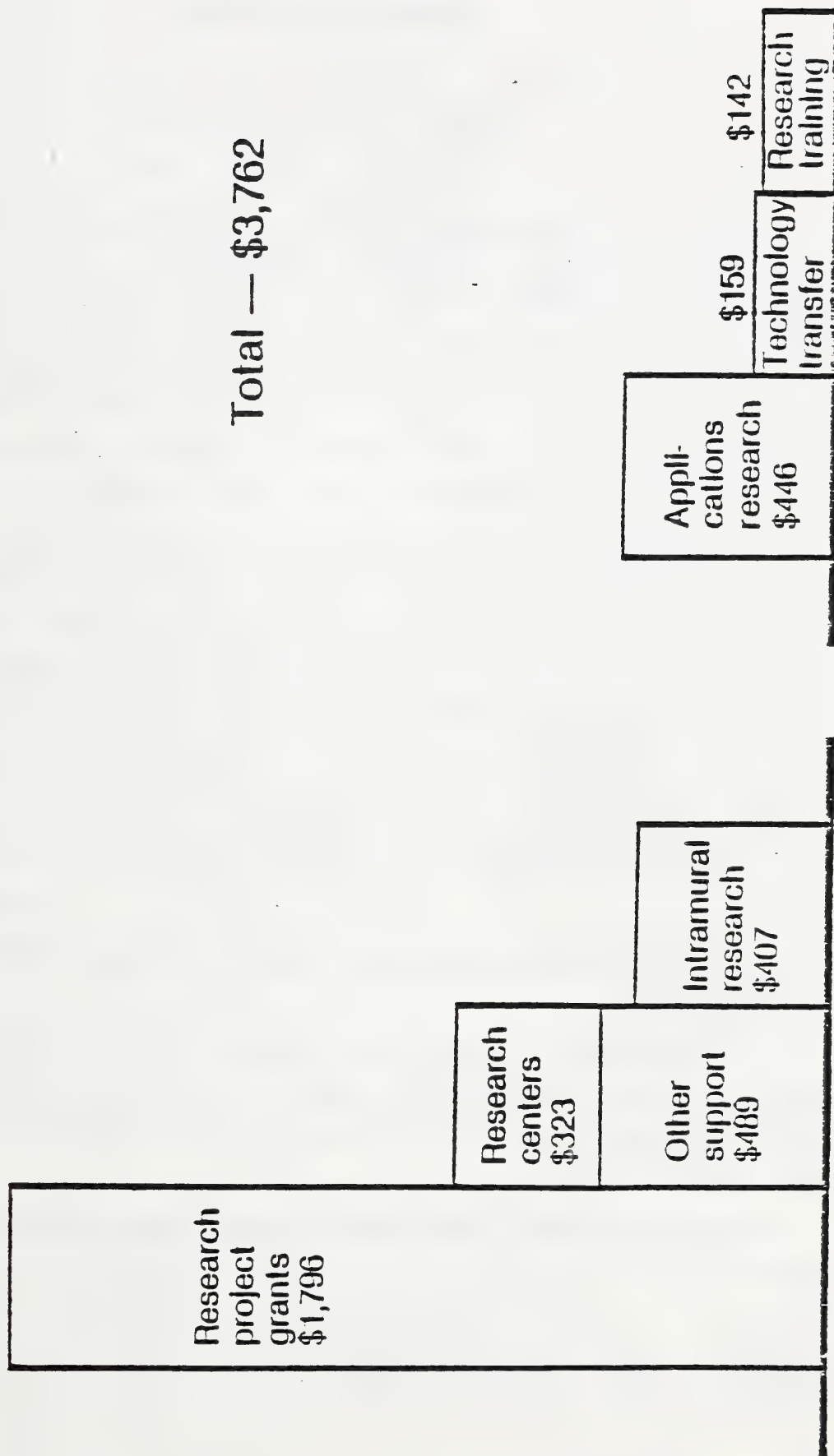
(IN MILLIONS)



\$3,762 Million

CHART 4

DISTRIBUTION OF NIH BUDGET, FY 1982 (IN MILLIONS)



Science base — \$3,015

THE ANFINSEN SERIES

by

Donald S. Fredrickson, M.D.*

Lately I've been having these nightmares. Anxiety dreams, I guess.

It's ten minutes past ten. You are late for the hearing. Your feet stick to the marble floors of the Rayburn, for these normally firm surfaces have turned into molasses. Your invaluable notebooks have come apart; the 500 sheets of budgets, opening statements, background notes and data, arranged under 75 tabs, are scattered behind you and nothing could get them assembled again. The Chairman, who has never missed a roll call, never been late—the Chairman who always begins promptly at ten—is waiting.

Somehow you get upstairs. The doors to the hearing room open. In the pit, down in front of the Chairman, yawns your empty chair. You arrive at it; practical and indifferent hands strap you in. You lift your eyes to the dais, but rising vapors obscure partially the Chairman's features. In them you see an amalgam of past and present. There is a rosette of venules on red cheeks, an impatient mood: Mr. John Fogarty, Democrat and bricklayer of Providence, Rhode Island, deceased in 1966. Now there is a hand like a cloven hoof, yellow hair streaming from nostrils to waxy points, white spats and a cape: Mr. Daniel Flood, Democrat and thespian of Wilkes-Barre, Pennsylvania, deposed in 1978. And there are also the ice-blue eyes and snow-white hair of Mr. William N. Natcher of Bowling Green, Kentucky, 28 years a Democratic Congressman, present Chairman of the Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies.

A brittle silence is broken by the voice of the Chairman—or is it that of the Chairmen? "Tell us now, Doctor, for the record, just what have you done with all that money over the last 30 years? What have you and your colleagues done with the 30 billion dollars, Doctor?"

You are awake again; today's dream mercifully dissolves, and the venue changes to tomorrow's.

* Director, National Institutes of Health, July 1975 - July 1981. Presently Scholar-In-Residence, National Academy of Sciences.

Tomorrow, the day after today, you are in that same catacomb--the Rayburn Building. This time, however, you are in the hearing room of the Committee on Science and Technology. It is hung with pictures of astronauts and satellites in outer space. This Committee is territory frequented by NASA and NSF. To NIH, which deals with the Labor and Health Committees, it is foreign (though usually friendly) territory. The Honorable Albert Gore, Jr., Chairman of a Subcommittee on Investigations and Oversight, will preside. Your opening statement will begin: "I am very pleased to be among those called to answer the committee's questions in this first of its hearings entitled Ethical and Institutional Considerations of Biomedical Research. Your letter of invitation, Mr. Chairman, describes your concern about recent episodes of falsification of research results. You state that you wish assurance that our scientific institutions are intact. . . ."

Dissolve.

Another day--not tomorrow, but someday soon--the venue will change again. We'll be in the Dirksen Building, in the "other House." The red eyes of television cameras peer into the blue-white circle of light. The tables are strewn with papers, the walls lined with further bundles of documents, loosely tied and sagging inward. Members of the staff are nesting in burrows hollowed out of these white drifts of paper sloping down from the windowsills. Senator Orrin Hatch of the Committee on Health will preside, with ace investigators conveying whispered secrets to the Chairman's ears. The hearing will probe contract procurement and conflicts of interest in the National Cancer Institute. As you watch, you think of Penguin Island and the 80,000 trusses of hay.(1)

This, too, shall pass.

I did not have such dreams in 1953, for I had come from Boston to Bethesda in a state of innocence. I had come to learn how to answer far different kinds of questions. I had been assigned, while still at the Massachusetts General, to the Anfinsen forces. When I arrived in Bethesda, they were bivouacked in Building Three, mobilizing for the capture of Building Ten from the contractors. The Era of Great Expansion was just beginning.

It was, actually, the second great expansion. Since this meeting is meant to follow our roots, and Anfinsen's, all deeply entwined with those of NIH, we may well go back still further. We will thereby gain an opportunity to pay tribute to some scientists and laymen, and certain events, involved in a quantum leap in science that has touched all our lives.

NIH, as most of its devotees know, began in a tiny Hygienic Laboratory in the Staten Island Marine Hospital in 1887. The Hygienic Laboratory moved to Washington four years later. As almost no one knows, it was to become the National Institutes of Health because of the single-minded crusade of one man, Joseph E. Ransdell (Fig. 1).

(Figure 1 about here)

In 1899 Joe Ransdell of Louisiana was elected to the House. He moved to the Senate in 1912, with the election of Woodrow Wilson to his first term as President.

In 1926 Ransdell introduced a bill (69th Cong., S. 4540) "To establish a National Institute of Health, to authorize increased appropriations for the Hygienic Laboratory, and to authorize the government to accept donations for use in ascertaining the cause, prevention, and cure of diseases affecting human beings, and for other purposes."

The Senator appears to have had in mind a dual mission. The new National Institute was to work on "the fundamental problems of the diseases of man," while the Hygienic Laboratory would continue to pursue "the solution of public health problems and . . . the coordination of research of public health officials and scientists." As Ransdell introduced successive bills over the next four years, the forms of his goal changed, but not the objectives. In 1930 Herbert Hoover signed his dream into law. Ironically, the Senator returned to Louisiana that year to run again and lost his seat to Huey Long. But he continued to seek support and contributions for NIH, with an office in Washington. At the end of Laborde's biography of Ransdell, the Senator is described as living back home on the plantation in 1951.(2) He died three years later nearing his 97th birthday. There should be placed at NIH a suitable reminder of its paternity.

The National Cancer Institute was created in 1937, and other divisions of the old Hygienic Laboratory were reestablished at Bethesda the following year as parts of a separate National Institute of Health. A table of organization proposed for the early NIH is shown in Fig. 2. The National Microbiological Institute is today's National Institute of Allergy and Infectious Diseases. The Experimental Biology and Medicine Institute has

(Figure 2 about here)

since been renamed four times. Today, as the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, it is quasi-host of this reunion.

Chris Anfinsen, after leaving the Heart Institute for Harvard, returned to the Arthritis Institute, where his laboratory is today. In July 1944 the Cancer Institute was reunited with NIH, which became the National Institutes of Health in June 1948.

In October 1940 President Franklin D. Roosevelt had come out to the campus to dedicate the NIH buildings rising there. New events were occurring at that time which would affect profoundly the future of NIH and biomedical science. Vannevar Bush, a trusted advisor to FDR during the war and a driving force in the Office of Scientific Research and Development (OSRD), strove to convince the Government that it must continue to put Federal money into the support of science after the war had ended. Bush proposed that this be done through a National Research Foundation (NRF). This would be a great umbrella organization, with all of science in one agency, including medicine. Senator Harley Kilgore had tried several times to start a National Science Foundation (NSF) along the lines of Bush's proposed NRF. The medical scientists, however, were strongly opposed to what they saw as an uneven match between biology and the other natural sciences. Their favorite for stewardship of biomedical research support was either the fledgling NIH or an independent Federal agency that might be called the National Foundation for Medical Research.(3)

In 1945 the war was coming to a close. The Federal agencies were auctioning off the unfinished contracts of OSRD. Professor Baird Hastings is in the audience today. He was not only the principal tutor of the guest of honor; he is also the sole surviving member of the OSRD Committee on Medical Research. He tells how, as the other scientific admirals and generals refused to bid, Rolla Eugene Dyer of NIH quietly picked up the good, unfinished projects to expand the NIH portfolio of research.

In April 1945, FDR died suddenly of a stroke. In July companion bills to create the NRF and NSF were submitted in the Congress. But in August the first atomic bombs were exploded over Japan; and during the rest of that session, the Congress had time for only the most urgent scientific matter on its mind—passage of an Atomic Energy Act to husband the promise and problems created by the New Physics.

In 1948 several new Institutes were created by law. Cancer was joined by Heart, Dental, and a year later by Mental Health. It was not until 1950 that President Truman signed a bill creating the National Science Foundation. By 1952, when the new agency received its first substantial appropriation—\$3.5 million—NIH was expending 15 times that amount. The concept of a continuum of biomedical research under the stewardship of a single agency, responsible for studies ranging from the most basic to the most applied, had become ascendant. It would prove to be an arrangement significantly

different from that of most other countries of the world, where the components of biomedical research and training have tended to be more scattered. There is no doubt that if one of the NRF or NSF bills had passed in 1945, NIH would today be a much smaller and largely clinical organization. Consolidation of health science into one institution, with separate appropriations by disease category, has undoubtedly meant more total support and greater expansion of American medical science.

Thus, the enormous influence of NIH-sponsored research on medicine and now the New Biology came about because of a chain of historical "accidents." As with so many of the events recorded in history, key persons (first Ransdell, later Lister Hill, John Fogarty, and many others) were in the right place (the U.S. Congress) at the right time. One may assume that, under different circumstances, the present biological revolution would take place somewhere and at some future date. It would also have its epicenter elsewhere. Clearly, some of us on this program today would be in another line of work.

C. B. Anfinsen was always regarded by those of us who were his older proteges as an M.D. (honoris causa). I think his achievements and influence would have been less spectacular had he not come to preside over the research training of so many young M.D.s (Clinical and Research Associates) in this hospital setting.

And what a remarkable setting it has been! I have been unable to discover who actually conceived of the Clinical Center. But it came into being under "Gene" Dyer, the sixth Director of NIH (Fig. 3). An anti-categorical man, Dyer shrugged off news of the

(Figure 3 about here)

creation of a Dental Institute by commenting, "I suppose we'll have to have an Anal Institute, too." This cynicism was accompanied by considerable wisdom and perseverance.

In the late '40s, excavation created a great mound of earth on the hill behind Building One, displacing the goats and other experimental animals housed there. The mound was often called Masur's Mountain, after Jack Masur, the first Director of the Clinical Center, who was another capable and stubborn architect of this unique hospital. The foundations were laid (Fig. 4), and a place for clinical research rose on a scale that

(Figure 4 about here)

was never imagined before. True, there was the Rockefeller Hospital in Manhattan, but

its complement of 40 beds was very modest. Here there would be 500. Nor was there anything in Europe at the time as a model of clinical investigation. The Pasteur Institute had no beds. Neither the Medical Research Council in England, the Max Planck Institutes in Germany, nor the Karolinska Institute in Stockholm had achieved the direct approximation of basic laboratories to the wards. The NIH Clinical Center became for clinical investigation what Gropius's Bauhaus in Dessau had once been for architecture.

(Figure 5 above here)

There were people who opposed the very idea. In 1952 or '53 Walter Bauer, Jackson Professor at Harvard, said to me when I told him where I was headed, "It's going to be the most gigantic backwater you ever saw." Ten years later Dr. Bauer came to Bethesda to recruit the new heads of most of his subspecialty units at the Massachusetts General Hospital. It is a pleasure to note here that the Jackson chair has just been refilled, this time by one of us on the program today. Dr. John Potts used to share my laboratory, and I made him the first chief resident of the Heart Institute before Bauer lured him back to Boston from the extraordinarily fecund "backwater" in Bethesda.

There were caustic comments, too, from our military colleagues across the street about the "Yellow Berets." The Clinical Center unquestionably permitted a fortunate but small percentage of medical academicians to maintain their skills during the doctor drafts for Korea and Vietnam. Had this not been so, several serious "generation gaps" would now be visible in the faculties of American medical schools, and the burst of molecular biology would likely still be some years ahead of us.

Why has the NIH intramural program been so successful? What were the ingredients and what were the proportions that turned out to be so effective?

Well, its unique size is important, of course. I came down from Harvard—most immediately, from the Mass General. There were excellent people there. Some were "giants," but there wasn't anything like the number of giants we encountered easily and frequently in Bethesda. One could go into the cold room on the first floor of Building Three, for example, and rev up the blender to make a tissue mince. Sure enough, Arthur Kornberg would come in and stare at the clumsy way you were handling things. He would be replaced by Bernard Horecker, who would turn off the improperly loaded blender. Earl Stadtman might come in right behind Horecker, asking why you had borrowed his blender. What could you do as a stumbling young ex-resident but absorb the free-floating energies from such a critical faculty? Young prima donnas learned indelibly that

attempts to evade the rules of evidence or to escape the rigors of the method were simply unthinkable.

The critical mass was there, enough experts to cover all the burgeoning paradigms of the time. It was said that after encountering some strange disease on morning rounds, one should have thought of the affected enzyme by noon, be in the laboratory of an expert on that enzyme by three, and be ready to discuss one's protocol to test for the deficiency at next morning's rounds.

The superb physical resources and the support systems were there, all aimed at a single purpose. There were no distractions or teaching obligations. There were, and still are, the extraordinary openness and freedom of exchange, the lack of compartmentation or destructive or inhibitory competition, and a sense of self-security that dissolves all the barriers to collaboration.

First and last, of course, were the people. There were the likes of Dyer, C. J. Van Slyke, Henry Sebrell, and Jim Shannon--the great recruiters. And then there were all the other people they recruited, who sorted themselves out according to chemical activities like elements on the atomic table. Those here today will find ourselves under the "Anfinsen series."

What kind of a man catalyzed the formation of the highly branched compound that was represented by his numerous laboratories? What were the energetics and the chemical activities definable in the long chain whose extension we are celebrating today? Each of us will see his reflection in the images we present to each other on this memorable occasion.

I can't say that Chris was a Geheimrat; certainly he was not the classic stereotype. I don't remember any didactic lessons in logic, method, or syntax. There wasn't any passing back of blue-penciled drafts of manuscripts, the kind of editing that some of us inflicted on our associates when we grew old enough to have them. Chris's direction was casual, sometimes diffident. He was a reluctant coauthor--at least, on my stuff. I think he was too eclectic to form a school. He was magnetic, though--a high-gauss type.

And we all sought his identification. We had a chance to grow fat, too, on the leftovers from his table. I remember that some of the best opportunities for recognition came from invitations to Chris that he didn't have time for and passed to us. Bob Gordon and I, for example, made our debut as "experts" on the biological aspects of fatty acid transport in doing one of Chris's chores for Physiological Reviews(4). It would have taken much longer to grow up in other surroundings.

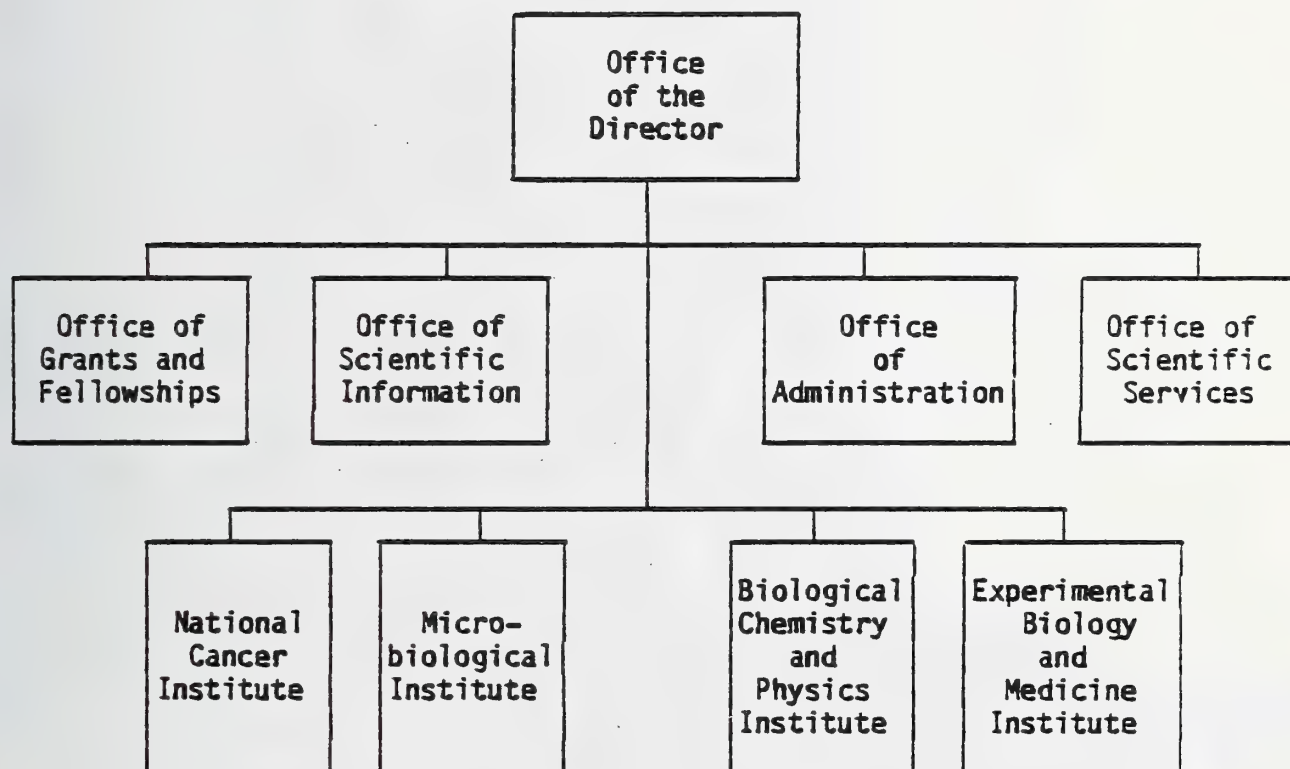
Thus, in a most offhand way, Chris proved to be a rare impresario, a convener of activated minds in large numbers. The old saying "The rich get richer. . . ." was operative. We owe the direction in which we traveled, and certainly a significant part of the distance gone, to the fact that we were allowed to discover who we were, and what science was all about, in his vicinity.

Like most of you, I wouldn't have traded that "search for reality" for a partner's share in Exxon or the Chase Manhattan Bank, or even a trip to the moon. For this, Chris, I want to thank you and say, "Happy Birthday!"

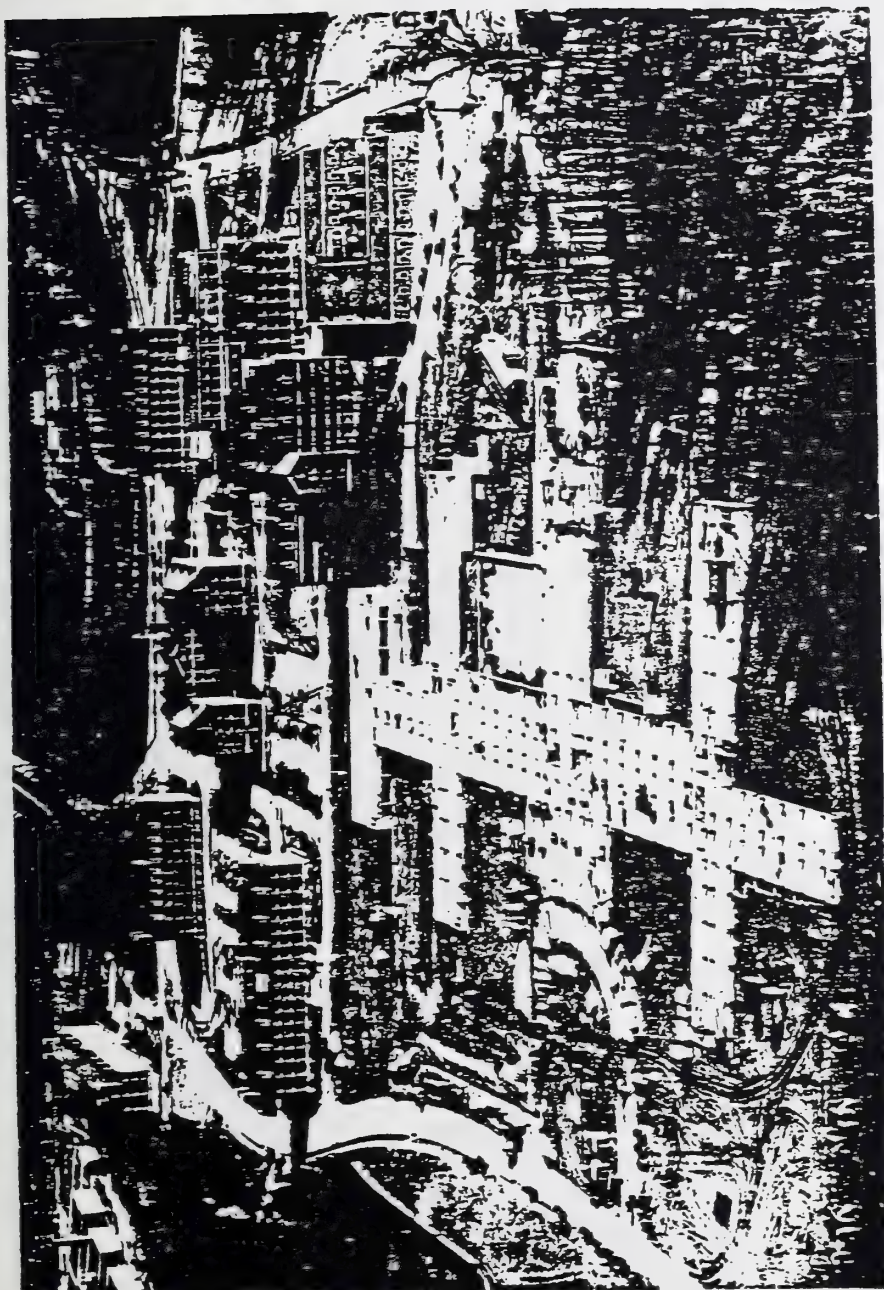
1. France, A.. Penguin Island (p. 171). New York: Random House, New York, 1909.
2. Laborde, Adras P. A National Southerner: Ransdell of Louisiana. New York: Benziger, 1951.
3. Bush, Vannevar. Science—the Endless Frontier. Washington, D.C.: Office of Emergency Management, OSRD, 1945. (Reprinted by NSF in May 1980.)
4. Fredrickson, D. S., and R. S. Gordon, Jr. Transport of fatty acids. Physiol. Rev. 38:585-630, 1958.

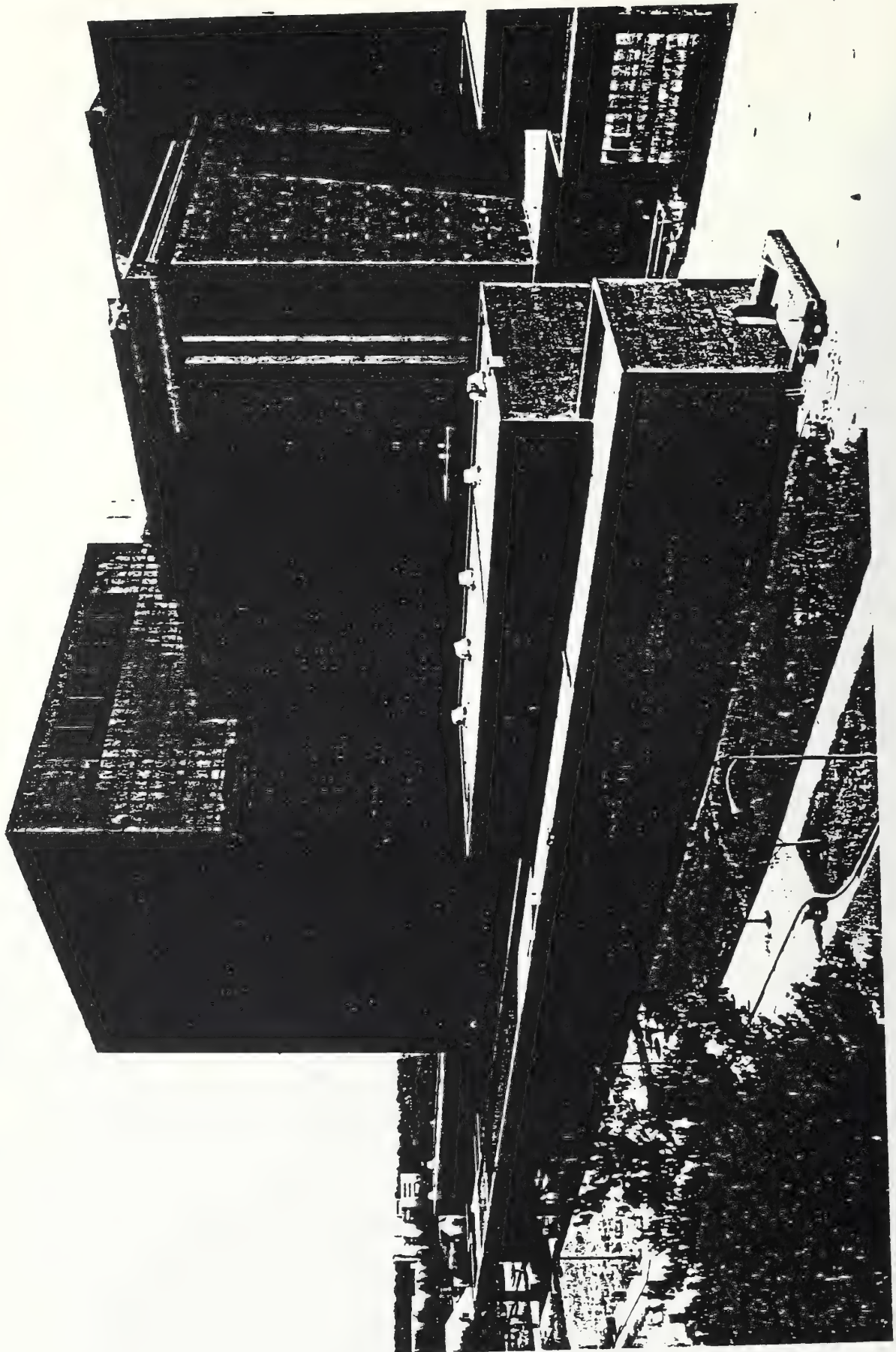


PROPOSED ORGANIZATION
FOR
NATIONAL INSTITUTE OF HEALTH
(1947)









STATEMENT

By

DONALD S. FREDRICKSON, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Before

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

COMMITTEE ON SCIENCE AND TECHNOLOGY

HOUSE OF REPRESENTATIVES

March 31, 1981

I am pleased, Mr. Chairman, to be among those called to answer the Committee's questions in this first of its hearings entitled "Ethical and Institutional Considerations of Biomedical Research." Your letter of invitation states that you are particularly concerned about recent episodes of falsification of research results, and that you wish to ensure both that our scientific institutions are intact and that the relevant Federal agencies are exercising their responsibilities.

I am here in a dual capacity. As Director of the National Institutes of Health, I represent the Federal agency which is the largest single source of Federal funds for support of biomedical research. As a scientist, I also have a member's share in the reputation of the profession.

The biomedical branch of the natural sciences is, of course, a good deal larger and older than the National Institutes of Health. The NIH in its present form began about 50 years ago. Physiology began about 1600, when Harvey was exploring the circulation. And you are aware, Mr. Chairman, that ancient clinical research takes us back to the beginning of written history, with an early flowering in the observations of the Greek physician, Hippocrates.

Our subject today is not the history of medicine or science, yet reference to the past is useful for perspective. From the beginning certain patterns inherent in science and scientists were visible and have persisted: intense competition for priority, a high premium on originality, the insistence that discoveries be greeted skeptically and accepted only after intensive examination, repetition and revalidation of the proofs. The rational, presumably value-free, system of judgment distinguishes the natural sciences from most other ways of deriving knowledge.

The "internal ethic" of science, the systemization of this rationalism, was established early. Occasional violations also did not wait long to begin. By "violations" I do not mean here, Mr. Chairman, the errors in observation or experimental design, or false deductions that occur frequently and are corrected by the very system we describe. These conflicts, which to outsiders may seem often to be arising in science, largely consist of this necessary part of the normal process, the shakedown of findings and conclusions until only the truth is left.

Instead, we are speaking today of violations of the scientific ethic. Among the lesser ones are false claims of priority or plagiarism. One has to read only a little of the sociological studies of science, for example, by scholars like Robert Merton, to realize that conflicts and quarrels over priority -- even charges of plagiarism -- have occurred over and over in science for hundreds of years. Such quarrels have even involved some of the greatest names in early science, like Galileo, Newton, and Descartes.

Mostly I presume, however, that we are here concerned with that most serious abuse, the fraudulent construction of experimental data. Cases of downright fraud in science have always been rare. Detection of some examples has taken many years, and revelations of old irregularities may be further expected. To give one startling example, modern statistical analyses have made it highly likely that some figures in Gregor Mendel's classic studies, an early window to modern genetics, could not possibly have been generated by the experiments. Whether these were intentional or unconscious errors, and whether they were Mendel's or his gardener's will never be known. Such questions and ambiguities surround most instances of scientific fraud. And some are never answerable.

I do not know, Mr. Chairman, whether scientific fraud, in less spectacular forms, occurs more frequently today than it has in the long history of science. There has been an exponential increase in the number of scientists practicing in the past 30 years over those working previously. The probability of some increase in abuses is therefore high. The likelihood of their being detected is also greater because of an increased density of peers and the development of ever more sophisticated techniques. The strength of the scientific process, however, and the dedication and vigilance of the institutions in which the standards of that process are maintained, do not appear to me to be weakened. Neither, in my opinion, is the public's huge investment in science endangered in any way. Indeed, the current production of useful new knowledge is nothing short of spectacular, and testifies to a vigorous state of health in the life sciences.

The occurrence of this hearing, however, may be taken as a reflection of some change in perceptions or interests of the public in science. With respect to biomedical research, a heightened concern was experienced six or seven years ago, when recombinant DNA technology raised questions about the power of the "new biology." Questions about the probity of science and scientists were inevitably part of this consciousness-raising.

The responsibility for standards and safeguarding the quality of biomedical research is spread among many social institutions. Let me turn first to the roles of NIH.

The first is its legal and fiduciary role as a Federal agency disbursing more than \$3.5 billion of public funds in Fiscal Year 1981 for the conduct and support of biomedical research. As such it must ensure that resources for science given by the public are used efficiently and productively, and that laws governing disbursement of Government funds are obeyed.

In the past several years NIH has developed new administrative procedures governing the conduct of research we support. This included promulgation last year of debarment regulations to extend to research grants penalties long inherent in research by contracts. At that time we began consultations with our advisory councils about the use of such a regulation and development of other administrative policies concerning any serious misbehavior in science. I understand that Dr. William Raub, NIH Associate Director for Extramural Research and Training, will appear before you later to describe our procedures in more detail. Key actors in this process include NIH's small but effective Division of Management Survey and Review, the auditors and Inspector General of the Department of Health and Human Services, the GAO, and the continuing oversight of the Congress.

Another role for NIH is the provision of part of the complex structure necessary both for the optimum functioning of the internal ethic and for the process of review that is important to quality control in science. The two-tiered peer review system of NIH, employing rotating panels of several thousand advisors -- both scientists and non-scientists -- in study sections and Councils, examines the proposals and the progress of most of the biomedical scientists in American universities as they recurrently compete for continuing support. This review concentrates more on proposals and progress than upon finished products of research. The latter are judged for quality and acceptability by a peer review system which lies in the private sector. It consists of fewer than 200 scientific journals which publish reports of original biomedical research only after critical review. The acceptance and publication of a piece of scientific work by these journals is of crucial importance. Science is existential. If research is not published, it has not -- for all practical purposes -- ever taken place, and the scientist can never claim priority or gain recognition for what he has done.

NIH underwrites most of the costs which the scientists it supports must bear for primary publication of their work. This occurs in non-profit journals, whose editorial boards and unpaid reviewers function as guardians of truth and judges of merit. No Government regulations or statutes govern the quality of this review; none are needed. When the report passes the gateway of these journals into the common domain, there begins another, endless review where the work will be read, considered, tested, and -- if it proves to be of true quality -- worked into the fabric of knowledge.

The institutional role of NIH in science continues in part through the help it gives to the nation's universities so that they will continue to be the traditional and essential places where the scientific method is taught and practiced. In the health sciences, NIH, again by peer review, selects certain scientists as recipients of funds for training and lays down requirements to assure preceptors and curricula of quality. The internal ethic of science is dependent upon the intellectual discipline and critical faculty which the young scientist absorbs as his training proceeds, and must be passed without diminution from generation to generation. Both in awarding specific training grants and in supporting the institutions for much of the costs they incur in providing the work-place for research, the public -- through NIH -- helps assure the preservation of high standards and a strong ethic in biomedical science in this country.

The cooperative arrangement between federal agencies and research institutions which NIH administers includes several networks of institutional committees which oversee research of special kinds. One network consists of institutional review boards (IRB's) which safeguard the adequacy of procedures to protect the rights and welfare of human subjects involved in research.

I should note here, Mr. Chairman, that appropriate involvement of human subjects is a special ethical area in biomedical research, in which NIH has taken a principal role. The first federal policy for experimentation involving humans was drawn up at the NIH Clinical Center in Bethesda in 1953. It was expanded to the entire Public Health Service in 1966 and provided the basis for codification of the Department of Health and Human Services (HHS) Regulations for the Protection of Human Subjects, which offer guidance to nearly all research institutions in the United States and many others throughout the world. The HHS regulations have been adapted to the program needs of 22 other federal agencies. The most recent revision of the regulations, prepared in the light of review by two Congressionally mandated commissions, was published on January 26, 1981. Obviously, human research ethics is a special, highly sensitive area, in which there can be no tolerance of fraud or other abuse.

Both the scientific community and NIH have responded to new technologies whose potential is unknown. It was academic scientists who convened the Asilomar Conference and urged their colleagues to delay some recombinant DNA experiments. NIH, at the urging of scientists, drafted guidelines for the conduct of such research. Nearly all universities, and many private sector laboratories, now have Institutional Biosafety Committees (IBC's). One of the tasks of these bodies is to oversee the use of recombinant DNA technology under the NIH Guidelines. Representatives of the IBC's meet regularly and a network is established which has a central focus at the NIH Office of Recombinant DNA Activities (ORDA) at NIH.

Violations of NIH human research regulations and recombinant DNA guidelines occasionally occur. It is in the best interests of the public that these matters be adjudicated first by the institutions -- the committees, faculties and administrators of the universities. It is technically true that

the institutions receive NIH grants, rather than the individual scientists; but the role of the university or similar institutions in maintenance of scientific ethics is greater and older than their fiducial relationships to government or newly required obedience to technical guidelines. The universities have always been primarily responsible for a scientist's access to laboratories and other resources maintained for the scientific community. Control of their staff appointments, tenure, and promotions is the real power of the university for the preservation of scientific ethics. The principal responsibility goes along with the ultimate power.

In my experience, Mr. Chairman, the academic communities are harsh in dealing with those who abuse the privilege of engaging in science. Expulsion from faculties and exclusion from laboratories, forms of excommunication for any scientist, are the common penalty for scientific fraud. Lesser offenses do not necessarily bring lesser penalties. Retention of faculty privilege but with loss of reputation as a scientist is a form of bankruptcy from which few scientists survive professionally.

Where its grants, or matters governed by IRB's or IBC's are involved, NIH also monitors the results of university decisions. Sometimes we add measures of our own, as was illustrated by recent NIH actions taken against a scientist violating the NIH Guidelines for Recombinant DNA Research.

To be sure, some observers see changing circumstances as increasing temptation to lower standards of conduct. One change often cited is the competition for grant funds. I am not sure this is so, for science has always been competitive.

It is also true that opportunity for scientists to profit from scientific discovery in biology appears to be rising. This suggests a change in

traditional values, dollars competing with priority, and other awards for originality, creativity, and significant discovery. The conversion of an open literature to a partly proprietary one because of patenting of such inventions as recombinant DNA technology could pose a serious threat to biology, but more probably in terms of reducing productivity and efficiency, rather than any increase in deceit. The penalties for fraud in patented discoveries will be compound: rejection by one's peers and prosecution by one's industrial patrons.

Let me complete my listing of roles for NIH in biomedical research by adding that it is also a bridge for communication between science and the public and, importantly, between science and the public's representatives in Congress. As explicator, it assumes a responsibility for providing up-to-date consensus on the state-of-the-art in biomedical research and technical consensus on health practices. As communicator, NIH must also be sensitive to changes in public perceptions of science, its ethics, as well as its power.

The NIH cannot guarantee the behavior of scientists or certify the quality of their work through independent analyses, fraud squads, or special statutes. Fortunately, none is necessary, for the natural sciences contain ultimate correctives for any debasement of the knowledge derived from research. Science is cumulative. It is like a building that is never finished. Any serious flaw in the foundation eventually will be revealed by the weight of the structure above it. If the extension of a wing shows faults in previous construction, the faults are corrected and the design changed. The rational nature of the scientific process makes this feasible and inevitable.

Despite any myths about selflessness, however, science is a thoroughly human endeavor. The creative drives of scientists have been much studied, but

no generalizations are sufficient to explain all deviations or failures to meet the rigid discipline and code of behavior demanded. The dangers, however, ultimately are not to the substance of science but to the scientists who are participants. The reaction of the scientific and academic communities to deviation from the paradigm is predictably human, too. A hint of scandal threatens all who work in the vineyard and the reactions are usually severe and unforgiving. Perhaps the most significant observation I can offer to your Committee is that I see no relaxations of standards or diminution in the quality control of natural science.

In summation, Mr. Chairman, I have reviewed the system of scientific inquiry as it relates to biology, medicine, and others among the so-called natural sciences. I have outlined the roles of NIH in relationship to this research. I also have expressed several personal opinions. One is that I do not believe there is an increase in fraud or other abuses of the scientific method in this work, and I know of no statistical evidence to confirm or deny this opinion. A second opinion is that the system contains safeguards which detect fraudulent data. And a third is that fraud in science carries severe personal penalties for the erring scientist -- punishments which are necessarily administered mainly by the scientific community itself -- and it is this feature of the system which is the ultimate deterrent.

REMARKS FOR DONALD S. FREDRICKSON, M.D.
DIRECTOR, NATIONAL INSTITUTES OF HEALTH
AT CEREMONY FOR
UNVEILING OF EXHIBIT HONORING CHARLES RICHARD DREW, M.D.
BETHESDA, MARYLAND
APRIL 10, 1981

MRS. DREW, DISTINGUISHED GUESTS, LADIES AND GENTLEMEN, IN 1974, DURING THE OBSERVANCE OF BLACK HISTORY WEEK, THE RECOMMENDATION WAS MADE THAT WE HONOR CHARLES RICHARD DREW FOR HIS DISTINGUISHED AND PIONEERING WORK IN BLOOD RESEARCH.

LATER, WE UNVEILED A PORTRAIT OF HIM BEFORE A LARGE AUDIENCE OF FAMILY, FRIENDS AND ADMIRERS IN THE NIH CLINICAL CENTER AUDITORIUM. TODAY, THAT PORTRAIT MAY BE SEEN IN THE NIH BLOOD BANK.

ABOUT A YEAR AGO, DURING A CEREMONY IN THE ROOSEVELT ROOM OF THE WHITE HOUSE, A BUST OF DR. DREW WAS PRESENTED TO THE "AMERICAN PEOPLE" BY DR. DONALD PARKS, CHAIRMAN OF THE CHARLES R. DREW AWARD COMMITTEE OF PHILADELPHIA.

IT WAS ACCEPTED BY VICE PRESIDENT WALTER R. MONDALE. THE BUST WAS FORWARDED TO NIH FOR DISPLAY. THE EXHIBIT WHICH WE ARE UNVEILING TODAY WAS ESPECIALLY CREATED FOR ITS DISPLAY. IT WAS DESIGNED TO GIVE VIEWERS, ESPECIALLY YOUNG VIEWERS,

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A GLIMPSE, THOUGH BRIEF, AT A MAN WHO HAD SO LITTLE TO START WITH BUT ACCOMPLISHED SO MUCH.

IT IS HOPED THAT THE EXHIBIT WILL INSPIRE YOUNG PEOPLE, BOTH MINORITY AND NONMINORITY, TO MAKE THE MOST OF THEIR LIVES--POSSIBLY, SELECTING A HEALTH CAREER.

MOST OF YOU PRESENT ARE AWARE THAT IN 1940 WHEN THE "PLASMA FOR BRITAIN" PROJECT WAS INITIATED BY THE BLOOD TRANSFUSION ASSOCIATION, THE COLLECTION OF BLOOD AND PREPARATION OF THE PLASMA WAS UNDER THE SUPERVISION OF DR. CHARLES DREW. DR. DREW SERVED THEN AS SUPERVISOR OF THE BOARD OF MEDICAL CONTROL'S BLOOD PLASMA DIVISION.

UNTIL THE MID-1900'S, BLOOD WAS ADMINISTERED TO A PATIENT THROUGH "DIRECT" TRANSFUSION. A BLOOD VESSEL OF THE DONOR WAS CONNECTED TO A BLOOD VESSEL OF THE PATIENT. ADVANCES IN TECHNIQUE PROGRESSED FROM THESE BEGINNINGS IN THE EARLY 1900'S TO THE EVENTUAL DEVELOPMENT OF "INDIRECT" TRANSFUSION--THE METHOD NOW IN USE. WITH INDIRECT TRANSFUSION CAME THE ADVENT OF BLOOD BANKING, UTILIZING TECHNIQUES OF COLLECTING AND STORING BLOOD FOR LATER USE.

DR. CHARLES DREW'S PIONEER WORK IN BLOOD BANKING, FOR THE PLASMA FOR BRITAIN PROGRAM, SERVED AS A GUIDE FOR SUBSEQUENT PRODUCTION OF BLOOD

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PLASMA AND LAID THE FOUNDATION FOR THE BLOOD PROGRAM OF THE AMERICAN RED CROSS.

BLOOD BANKING IS NOW AN INDISPENSIBLE MEDICAL RESOURCE. TODAY, AND EVERYDAY MORE THAN 18 THOUSAND PINTS OF BLOOD ARE TRANSFUSED IN THE UNITED STATES, OR APPROXIMATELY SEVEN MILLION PINTS A YEAR. AND WITH ADVANCES IN MEDICAL CARE, THE NEED FOR BLOOD HAS MORE THAN TRIPLED JUST IN THE LAST TEN YEARS.

AND QUITE NATURALLY, KNOWLEDGE ABOUT BLOOD IS IMPORTANT FOR ALL SCIENTISTS ENGAGED IN BIOMEDICAL RESEARCH. MY OWN INTEREST IN BLOOD RESEARCH BECAME MORE INTENSE WITH MY ASSOCIATION WITH NIH'S NATIONAL HEART INSTITUTE SOME 20 YEARS AGO.

NATURALLY, BLOOD IS IMPORTANT TO US AT NIH. MEMBERS OF THE BLOOD BANK DEPARTMENT LOCATED IN THE CLINICAL CENTER HAVE MADE MAJOR CONTRIBUTIONS IN PRACTICAL BLOOD BANKING TECHNIQUES AND BLOOD RESEARCH. BESIDES SUPPLYING BLOOD AND BLOOD PRODUCTS TO THE CLINICAL CENTER, THE BLOOD BANK IS ALSO A CENTER FOR RESEARCH ON BLOOD DISEASES AND HEPATITIS AND A TRAINING INSTITUTION FOR PHYSICIANS, NURSES, AND TECHNOLOGISTS.

TODAY, FRIDAY, APRIL 10TH, WE ARE INDEBTED TO THOSE MANY PIONEERS BEHIND THE SCHEDULED FIRST FLIGHT OF OUR SPACE SHUTTLE.

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AND TODAY WE ARE INDEED INDEBTED TO CHARLES DREW AND HIS PIONEERING WORK AND THOSE MANY RESEARCH PIONEERS WHO CAME BEFORE HIM AND THOSE WHO HAVE COME AFTER HIM.

BUT WHAT ABOUT THIS PHYSICIAN, THIS MAN, A FATHER, HUSBAND, SURGEON, SCIENTIST, TEACHER AND ATHLETE? MUCH HAS BEEN WRITTEN ABOUT HIM. MUCH COULD BE SAID ABOUT HIM. POSSIBLY, DURING THE SHORT TIME WE HAVE HERE THIS MORNING, A CITATION HE RECEIVED COULD SERVE TO SUMMARIZE A DEDICATED CAREER THAT WAS ALL TOO BRIEF. I QUOTE FROM THE CITATION FOR THE AWARD OF THE DEGREE, DOCTOR OF SCIENCE, TO DR. DREW BY AMHERST COLLEGE, DATED JUNE 15, 1947:

"GRADUATE OF AMHERST IN THE CLASS OF 1926. OUTSTANDING ATHLETE OF THE DECADE OF THE 1920'S; WINNER OF PRIZES, HONORS, TROPHIES, AND AWARDS WITHOUT NUMBER AT AMHERST AND MCGILL. ROCKEFELLER FOUNDATION FELLOW IN SURGERY. BRILLIANT INVESTIGATOR OF THE PROBLEM OF BLOOD AND PLASMA PRESERVATION: YOU WERE CHOSEN UNANIMOUSLY DIRECTOR OF THE PLASMA PROJECT FOR GREAT BRITAIN IN THE DARK MONTHS WHICH FOLLOWED DUNKIRK. DIRECTOR OF THE FIRST AMERICAN RED CROSS PLASMA BANK. ASSISTANT DIRECTOR OF BLOOD PROCUREMENT FOR THE NATIONAL RESEARCH COUNCIL. WINNER OF THE SPINGARN MEDAL. AUTHOR OF FOURTEEN LEARNED BOOKS AND ARTICLES. NOW PROFESSOR AND HEAD OF THE DEPARTMENT OF SURGERY AT HOWARD UNIVERSITY AND CHIEF SURGEON AND MEDICAL OFFICER OF FREEDMAN'S HOSPITAL. YOUR GENIUS AND YOUR DEVOTION HAVE SAVED THE LIVES OF TENS OF THOUSANDS."

NEED WE SAY MORE?

IT IS WITH A GREAT DEAL OF PLEASURE THAT I WELCOME EACH OF YOU TO THE NATIONAL INSTITUTES OF HEALTH AND TO THIS CEREMONY.

Communal Resources, Community Responsibilities

DONALD S. FREDRICKSON

We found ourselves recently in the auditorium of a private museum in Baltimore. It was a meeting of the Interurban and the Peripatetic Clubs: two anachronisms of communication conceived in Osler's time to keep the academic centers of the American Northeast in intellectual parity. Despite the advantages of vast plenary sessions, there remains a need for more intimate and leisurely opportunities to muse upon the state of our art. On this particular morning in the museum, things were moving slowly and unremarkably toward the midmorning coffee break. Myron Weissfeldt of the Department of Medicine at Hopkins was talking about closed-chest cardiac massage. Could there really be anything new, I wondered, on the subject of cardiopulmonary resuscitation? Suddenly, Resusci-Anne®, the CPR dummy, took a tremendous breath and blew over a durable old hypothesis. We were in the midst of one of those crises of Thomas Kuhn's,¹ feeling the seismic prelude to the shifting of a scientific paradigm.

The mouth-breathing part of CPR is as old as the Book of Kings II, where Elisha's story of reviving a child by this method appears briefly. More than 20 years have passed since Kouwenhoven and Knickerbocker² made us all conscious of closed-chest cardiac massage. How simple is this miraculous gift, the rhythmic squeezing of a stilled heart between the sternum and the spine to make it pump blood again.³ Any physician, every conscientious paramedic, all the nurses can tell you how it works. Now suddenly we discover that the explanation is wrong!

The heart, it seems, cannot be made to beat mechanically by pushing it or squeezing it from without. Cardiac massage, it turns out, is really artificial respiration. Blood is moved to the

periphery because of changes in intrathoracic pressure. Rhythmic pressure differences become the pump, and the valves in the peripheral veins, rather than those in the heart, serve to maintain artificial circulation.⁴

This overturning of conventional (nay, classical—Harveian) dogma has a symbolic significance for clinical investigators—indeed, for all who admire the beauty of the scientific method. The few skeptics who stubbornly refused to ignore anomalies left unexplained by the prevailing logic have allowed virtue—and reason—to triumph again. We all owe a debt to these colleagues who have been persistently trimming the edges of well-plowed fields somewhat removed from the present revolution in biology. They have reminded us that we will never comprehend living systems without ceaseless refinement and reordering to explain anomalous observations.

That some of us are permitted to make a paid profession of tilting at these constant and fascinating challenges is one of the redeeming features of our imperfect culture. I believe the continuance of the opportunity to work at expanding the scientific base of medicine is assured. Society has agreed to underwrite the task indefinitely, if only because of the protection and benefit to its members. The terms of the contract between society and the scientists, however, are annually renewable and subject to change.

Stabilization of Research Funding

In a recent issue of the *New England Journal of Medicine*,⁵ I had the opportunity to offer some thoughts on the exuberant condition of the biomedical sciences and their present confrontation with the "dismal science" of economics. The Administration and the Congress are now engaged in deep debates on the federal budget. With many other social programs, the support of biomedical science is largely dependent on this purse. I can state objectively that in their preparation and consideration of the budget, the

Public Policy Address delivered to the 38th Annual Meeting of the American Federation for Clinical Research on April 26, 1981.

Dr. Fredrickson was Director of the National Institutes of Health from July 1975 to July 1981.

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President, Secretary Schweiker, and the Congress have demonstrated that they understand the dependence of basic biomedical research on support from the state. They have attempted to spare science and the institutions from seriously harmful budget reductions in the current heroic attempts to control federal spending.

The universities are highly dependent on the federal government for support of health R&D. NIH now provides over 60% of the total (Figure 1). For over 20 years the proportion of such support supplied by industry has not been more than 2 or 3%. Not in 30 years have we faced a greater need for prudence in using the resources at our disposal. Our scientific community needs to have a clear understanding of how best to play what I have referred to elsewhere⁵ as a *zero sum game* of allocation.

Joseph A. Califano, Jr., speaking to this meeting in 1978 as Secretary of Health, Education, and Welfare, proposed the setting of a five-year plan for the funding of health research. The first step was to be an examination of the principles upon which federal funds are used to support biomedical research. In October 1978 we rearticulated such principles at a public meeting in Bethesda.⁶ Investigator-initiated research was judged to be the avenue most likely to yield new discoveries that would eventually benefit the greatest numbers. Such research includes high-risk, long-term basic research, for which federal support is irreplaceable. Investigator-initiated research is supported by several mechanisms, some of which are shown in Figure 2. Over 75% of all NIH resources are devoted to activities in the *Science Base* category. The prominent left-hand bar—research project grants—represents the mechanism that has been given highest priority in budget planning for the last four years.

Approximately 16,000 research project grants are in effect at the present time. You may also be aware that during the last several years the Congress and the Administration have reached general agreement to stabilize the capacity to fund a minimum number of new and competing grants each year, approximately one-third of the 16,000. In fiscal year 1980, 4,750 such new and competing awards were made. The President's budget in 1981 permits the funding of approximately 4,800, and the budget for 1982 includes capacity to fund 4,900, even at the expected

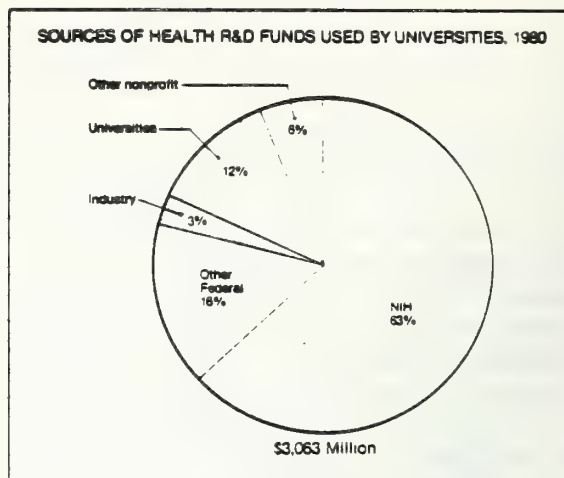


Figure 1. Universities in 1980 used R&D funds estimated at \$3,063 million. Of this, an estimated \$2,413 million—nearly 80%—was in federal grants and contracts, including \$1,935 million from NIH. Support from industrial sources accounted for \$78 million, about 2.6%. In 1960 universities used about \$320 million for health R&D, and in 1969 about \$1,042 million.

increase in the cost of such grants due to inflation.

This stabilization of the ability to fund a fairly constant number of grants is of great importance in reassuring investigators of the continuity of support for this type of research activity. It is a stability, however, that has been purchased at some cost to other mechanisms for funding research. In fiscal year 1979, research project grants represented approximately 44% of the total obligations of NIH. In fiscal years 1981 and '82, that proportion will have risen to 50%. Several of the Institutes are concerned that other aspects of the research programs are now being taxed to the limit in order to maintain the capacity for funding new and competing grants within the appropriations or continuing resolutions under which NIH has operated for the last several years.

At the opposite end of this functional display is a much smaller bar, which represents the training funded by NIH under the National Research Services Authority. In 1980, approximately 5% of each NIH dollar was allotted to training under NRSA. At one time in the middle sixties, the figure was closer to 25 cents for each dollar. Since that time there has been a slow but progressive drop in the overall proportion and total allocation for training and the total number of trainees supported by either institutional

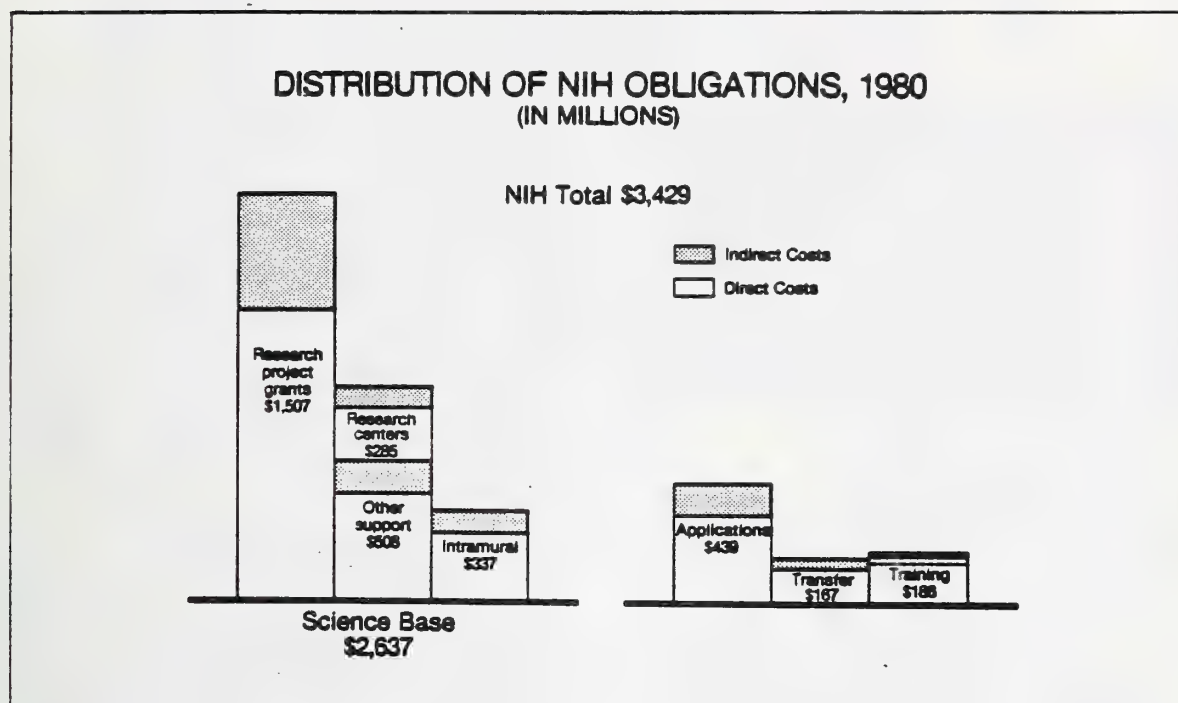


Figure 2. NIH Obligations for fiscal 1980 are here distributed according to a budget mechanism called SATT, acronym for Science base, clinical Applications, technology Transfer, and research Training. The shaded portions of the bars represent indirect costs for which the investigators' institutions are reimbursed. In the bar for training, the portion above the dotted line represents institutional training allowances.

training grants or fellowships, which are both represented in this bar.

Part of the reason for this decline is that the growth of the academic biomedical research system has nearly ceased. There also have been differences of opinion between the Administration and the Congress on the need to maintain federal support for training in the biomedical sciences. The President's budget for fiscal years 1981 and '82 requires a modest reduction in the number of trainees from approximately 10,600 full-time equivalents to 10,000 supported in each of the two years. There is, however, a much greater reduction in the total budget proposed for training in that the Administration has moved to eliminate the 8% indirect costs and the larger (approximately 22%) institutional allowances that have been part of these grants for many years. The institutional allowances are awarded to the institution to cover the cost of faculty salaries directly related to the training function, the cost of supplies and travel, and certain other expenses deemed necessary to maintain the quality and necessary enrichment of the curriculum.

The mention of indirect costs under training should encourage us to examine another important question of the balance between individual and institutional support that is represented by the projection of the NIH budget. You will note that a portion of each of the bars in Figure 2 is shaded at the top. This represents the indirect costs recovered in addition to the direct costs of such research. There is much misunderstanding between faculties and their university administrations, and between government research supporters and the federal auditors and others who set rates and determine the portion of cost-sharing that underlies the support of institutional research activities.⁷ The Government recognizes indirect costs as real costs for which the universities need to be reimbursed. At the same time some academic scientists eye suspiciously any progressive increase in indirect costs as representing a "steal" from the purse available to support their research.

During the last year and a half, and particularly through activities of the Director's Advisory Committee,⁸ NIH has been examining carefully the anatomy of indirect costs. We have repeated-

ly brought all sides together in ecumenical efforts to reach appropriate understanding of how these costs should be treated. Part of a new initiative to maintain the appropriate balance in these shared costs is the consideration of fixed obligation grants, which might include negotiation of both direct and indirect costs in a single, fixed sum. One of the advantages of such a grant could be a considerable reduction in time-and-effort accounting now required by the Government (under OMB Circular A-21).

Categorical v. Communal

Another most important consideration in the total spectrum of NIH support for science is the balance between the categorical programs and what we shall call here communal or community resources. The categorical nature of NIH is part of the genius of its traditional organization. Each of the Institutes, most of them assigned responsibilities with either disease or organ-system orientation, provides both the specific expertise and the parochialism required to assure that knowledge relating to specific health problems is stubbornly pursued until practical inventions result in prevention or bring desired relief to sufferers. The Institutes may be said to have high centrifugal force derived from their speed and independent suspension. Their natural tendency is to pull away autonomously from constraints imposed by the NIH center, and from the solidarity of a single universe of knowledge about man and his health and diseases. Still, the essential unity cannot be avoided in the efforts to remove ignorance about life and about ourselves. Significant new knowledge applicable to one sector of work often comes from another. As the work proceeds, the boundaries between the Institutes tend to be eroded. Indeed, sometimes inexplicable asymmetry in the distribution of resources to the several Institutes is partially offset by what I call the *Venetian principle*. The categorical, highly individual nature of Institutes may be gloriously visible on the surface, like some of the structures in Venice—the Cancer Campanile, the Doge's Palace for Heart, Lung, and Blood, etc. Beneath them all, the foundation is continuous and completely miscible. All the Institutes add to the support of common basic knowledge, reaching far beyond their immediate area. Some persons who are weary of my metaphors have reminded me that Venice is

sinking. I take pleasure in retorting that, on the contrary, the water (insofar as it is fundamental knowledge) is rising.

The individual Institutes also have a common dependence on the capability of the same extramural institutions to carry out their research. Their overall interests cannot be served solely by categorical or narrow project support. There is growing need for improved and increased "trans-NIH" attention to research resources in the communal sense. Sharing of facilities and instrumentation is required both to respond to shortages and to maintain institutional vigor.

The basic idea is not new at NIH. For nearly 20 years, there has been a single large Division of Research Resources (DRR) to carry responsibility for several such programs. Certain others are maintained in our Institute of General Medical Sciences and our Division of Research Services. The purchasing power for DRR has been declining steadily over the past decade as categorical mandates have occupied the principal attention of the Congress. We have succeeded in stopping that slide, but now, with increasing pressure on the budget, a need is arising for new mechanisms to preserve institutional support. The Institutes need to take a special corporate interest in preserving the essential parts of these communal resources.

One of DRR's most important activities is the Clinical Research Centers Program which ensures opportunity for clinical investigations in major institutions. Presently the research activities of some 3,700 investigators supported by more than 2,000 research grants—at an annual total of over \$270 million—are centered in these clinical research facilities, which continue to represent an example of efficient, shared support of research. Similarly, DRR's Biotechnology Resources Program provides instrumentation serving over 2,000 investigators, who last year were conducting 1,096 research projects with \$128 million in NIH grants. Almost 1,000 investigators used the Animal Resources and Primate Centers in conducting 427 research projects with \$51 million in NIH support.

Another highly specialized community resource is the National Library of Medicine (Figure 3). It is the center of a communications network uniting biomedicine the world over. Its capacity to handle the information flow must be

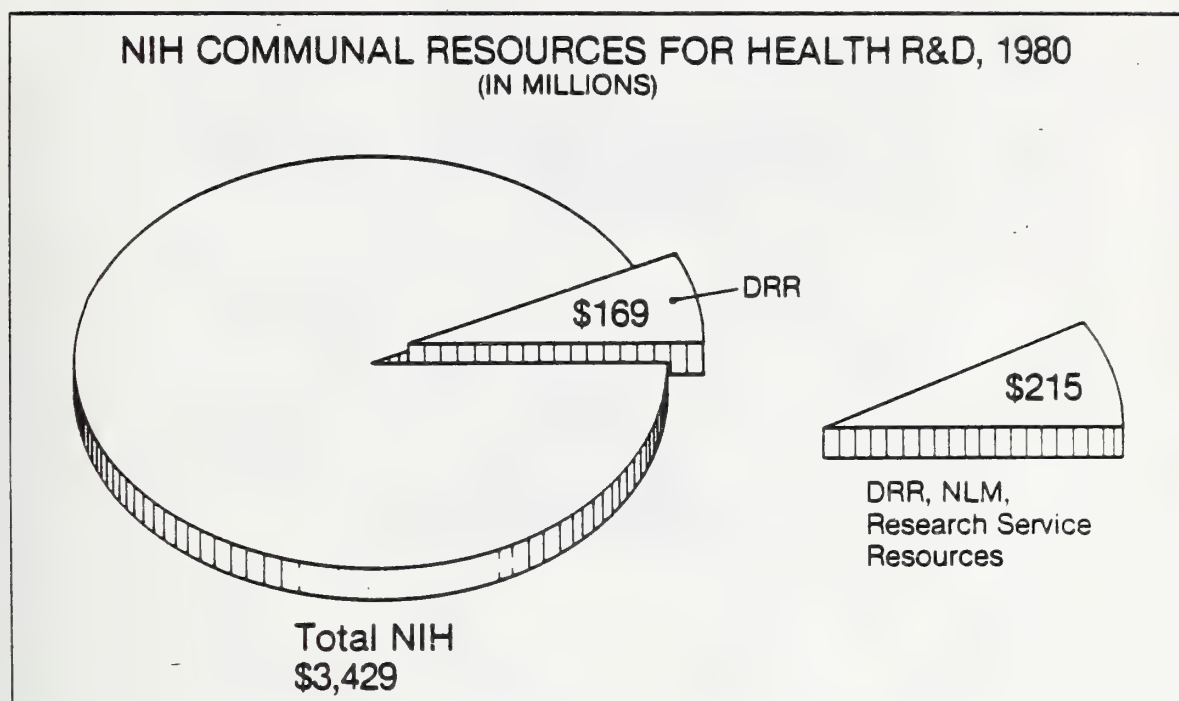


Figure 3. The Division of Research Resources, NIH, awarded \$169 million in fiscal 1980 for resources shared by the health research community: clinical centers, biotechnology research, laboratory animal sciences, biomedical research support (general), minority biomedical support, etc. Other NIH communal resources, adding \$46 million, included the National Library of Medicine and such research service resources as the American Type Culture Collection.

maintained in a time of no growth in federal funding for the aggregate biomedical research enterprise. Other community activities maintain invaluable linkages between the past and the present, such as type-culture collections and special holdings of genetic strains in cells or in research animals. These, like special data banks of polypeptide or polynucleotide sequences, must serve all of biology, and thus require community participation and preservation.

Indeed, we must now ask whether some of the more sizable investments of a given Institute should become the subject of corporate decision-making. I refer here, for example, to large clinical trials (Figure 4). The several Institutes of NIH have some \$177 million invested. Some of these projects represent commitments of \$5 to \$10 million per year. Once they have begun, such trials may require \$50 to \$100 million per project over periods of 10 years or more to ensure definitive results. The drain on the annual pool of available resources posed by these major investments means that selection of trials to be undertaken will require a more cooperative review than in years past. Trade-offs have to be selected objectively, and overall priority deci-

sions can no longer arise solely by competition for charisma among narrow sectors of the research community. The technical review will need to be presented to the Administration and the Congress for their final decisions.

Difficult community decisions will also have to be made about research training (Figure 5)—long an activity oriented programmatically within each of the Institutes. This is a matter of particular importance to clinical investigation. We are all alarmed by forecasts of declining numbers of the clinical scientists who must participate at some stage in research that has as its aim the improvement of human health. Combined MD-PhD training programs are communal assets. So, indeed are all training programs when planning is required to meet future needs for supplying clinical investigators and to assure simultaneously the continued training of nonclinical scientists who bear a proportionately larger share of sophisticated inquiry than was true a decade or two ago.

The essential need is for decision-making that will preserve healthy competition and the vitality of scientific inquiry within whatever total sum of resources is available for that purpose. As part of

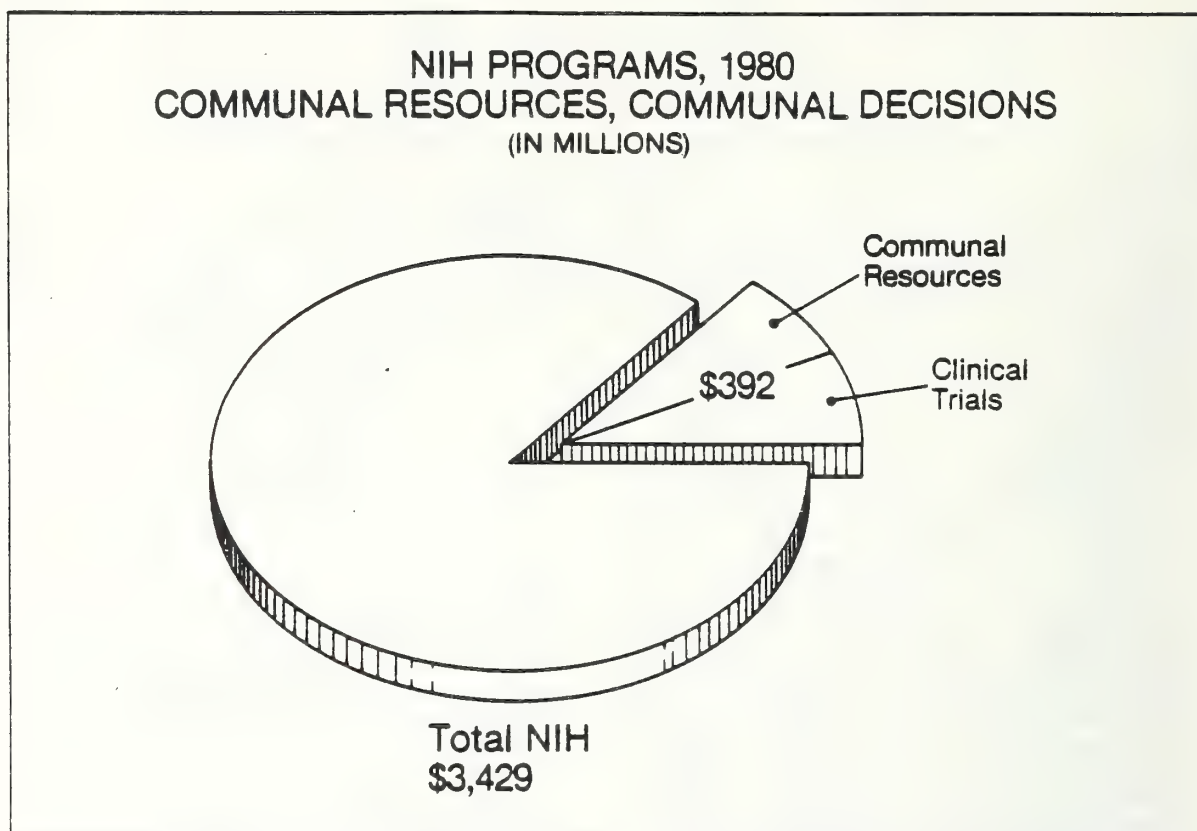


Figure 4. NIH awarded \$215 million for resources to the biomedical research community in fiscal 1980 (see Figure 3). Large-scale clinical trials call for some priority-setting communal decisions because of their high cost and the need for broad consensus in design. NIH-supported clinical trials active in 1980 totaled about \$177 million.

the changing times, then, some kind of augmented national research resources program will be critical for the continued health of categorical research in universities, academic medical centers, and federal laboratories, including the intramural program of NIH. The technical details and trade-offs in any such plan must arise from a consensus of experts whose productivity depends on it. Once properly arrayed, the final choices will be made by representatives of those who pay. An informed scientific community that understands its own political support, social organization, and economic foundation is crucial now for maintenance of the Enlightenment.

The Science Ethic

We have to be concerned with full participation of the scientific community in issues other than the husbandry of resources to support research. We need to be sensitive to changes in attitudes about science. The *new biology*, particularly the emergence of recombinant DNA

technology, has occasioned some new public interests and perceptions. This consciousness-raising has included questions about the probity of science and scientists.

Recently several of us were summoned to appear before the House Subcommittee on Investigations and Oversight, a body of the Committee on Science and Technology. The Chairman, Mr. Albert Gore, and his committee intend to hold a series of such hearings this year: "Ethical and Institutional Considerations of Biomedical Research." The subject of this session was violations of the scientific ethic.

Faced with the prospects of cross-examination, under oath, about misbehavior in his own profession, one prepares with some introspection. The immediate compulsion to bone up on the grand Hegelian syntheses of the professional ethicists must be resisted. They often seem to miss the point. But then, some of the writings of our own prophets are not too helpful either. Jacques Monod,⁹ for example, in *Chance and*

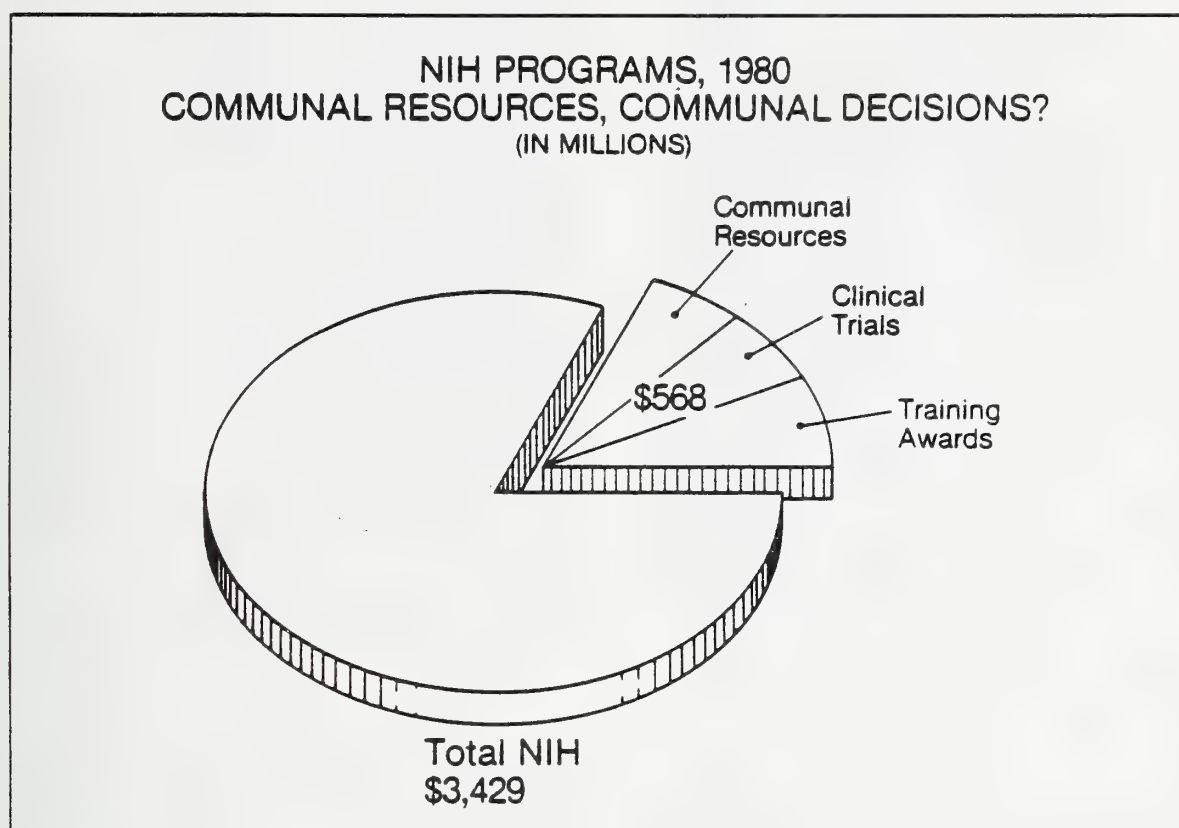


Figure 5. The biomedical research community may need to make collective decisions on research training as well as on clinical trials. Over the past decade obligations for these programs have been erratic, ranging from \$185 million in 1972 to \$120 million in 1976. The 1980 level was \$176 million.

Necessity, defends brilliantly the purity of the scientific method, yet his tone suggests that he would view as apostate anyone who would discuss so private a matter with members of the Congress.

Preparation for such an encounter ought to include other readings. *The Piltdown Forgery*¹⁰ might be a place to start. Certainly another perusal of *The Case of the Midwife Toad*¹¹ is mandatory. Perhaps, for historical perspective, one should flip through Babbage's¹² dismal treatise on fraud in English science in 1830. A few hours' absorption with Thomas Kuhn¹ can bring back any lost wonder at the method of science, and the counsel of Robert Merton¹³ will restore faith in its normative structure.

Above all, one cannot allow critics to forget that science is a thoroughly human endeavor. The necessary creativity, originality, and drive for recognition have to be reined by strong intellectual discipline and emotional stability. Occasionally the proper balance is lost.

I do not know whether breaches of ethic are more common today than at other times in the relatively long history of science. The number of scientists practicing now is several orders of magnitude greater than even 30 years ago, and the probability of some absolute increase in abuses of privilege is therefore high. Nevertheless, I do not sense any diminution in the strength of the scientific process and the effectiveness of its self-contained correctives to deal with flaws in scientific substance.

The dedication and vigilance of the institutions in which the process is taught and the standards maintained do not appear to me to be weakening. The universities and the scientific communities have, indeed, borne gracefully an increasing array of special requirements to oversee research. All of you have to deal with the Institutional Review Boards (IRBs), which safeguard the rights and welfare of persons who are subjects of clinical investigation. The HHS regulations providing protections for human

research subjects have recently been revised and clarified. There is no expectation that they will ever disappear, for they perform an essential function. From time to time, however, ethical issues arise that transcend the boundaries of local research projects and concern the entire research community. Such issues may be thrust upon us by expanding technologies that can arouse unusual public anxiety.

A central focus for the network of IRBs exists in the NIH Office for Protection from Research Risks. The small staff serves well in a difficult role. That office is now considering how best to create or identify a forum for resolution of the occasional new, very difficult questions concerning ethics of human research. Proposals to apply some of the new techniques may exceed the capacity of any single IRB, given that the decision may seriously perturb public perceptions of science. Examples are the proposed trial of devices to replace the entire human heart or experiments constructed to revise the human genome.

When such problems are not amenable to legal solution and become the province of bodies constructed along political lines, the public interest may be badly served. A lesson is available, however, in how difficult questions—bearing directly on the conduct of science—can be handled. We are now in the sixth year of self-imposed restrictions on the use of recombinant DNA technology. These Guidelines are also administered locally through Institutional Biosafety Committees, organized in nearly every university and many private-sector laboratories.

An unusual and effective focus for the network of the Biosafety Committees has been provided by the Recombinant Advisory Committee. The RAC is a central forum where the responsibilities of the scientific community can be shared with the public. Its purposes are continuous change of the Guidelines in accordance with the swift evolution of scientific knowledge and the adjudication of questions about interpretation. The principal features of the RAC are: a mixed membership in which scientists with the highest technical qualifications work with others, including laymen, of broad interests and concerns; the restriction of engagement to specific proposals, as opposed to debate on abstractions; and the use of open meetings with visible agendas and adequate opportunity for public comment on

important decisions before their promulgation. The RAC does its work in ways that might be emulated for coping with knotty universal questions about clinical experimentation.

However, we do not necessarily need new bodies for decisions or recommendations concerning community responsibilities in biomedical research before we have exhausted the possibilities of some we have already chartered, such as the NIH Study Sections and National Advisory Councils.

We now face the setting of some new precedents in regard to responsibilities of the scientific community. These deal with occasional deliberate, serious breaches of human research regulations, of recombinant DNA Guidelines, and of other embodiments of the scientific ethic—infractions not representing violations of criminal statutes. It is in the best interests of the public, and of the scientific community, that these matters be adjudicated first by the committees, faculties, and administrators of the universities.

It is technically true that the institutions receive NIH grants, rather than the individual scientists; but the role of the university or similar institutions in maintenance of scientific ethics is greater and older than their fiducial relationships to government or their newly required obedience to technical guidelines. The universities are primarily responsible for a scientist's access to the laboratories and other resources they maintain for the scientific community. Control of their staff appointments, tenure, and promotions is the real power of the university for the preservation of scientific ethics. The principal responsibility goes along with the ultimate power.

We have been reminded by several recent experiences, however, that resolution of the injuries related to misbehavior cannot always be achieved solely within the academic institution of the scientist. An investigation of the fiducial elements will require the presence of the federal funding agency. The interests of the scientist at the center of allegations may also need to be protected by third-party participation. Perhaps most seriously, the prestige and reputation of all who work in the vineyard can be so diminished or threatened by one member that community response is required. NIH sometimes must act as agent for both the public and the scientific

community in fulfillment of these responsibilities. New HHS debarment provisions have recently been discussed with the National Advisory Councils. The implementation of these rules is evolving with the deliberateness and great care required of any disciplinary actions that may affect the access of a scientist to his profession, or deprive the world of his services.

I impart this information to assure you that new procedural precedents will be set with a deep concern that no harm be done to the basic process and appropriate freedoms of scientific inquiry. However, the preservation of biomedical research and clinical investigation—so remarkably placed to benefit mankind—depends not only upon economic support from the public funds. It also requires the continued respect and confidence of the society it serves.

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Welcoming Statement *

Donald S. Fredrickson, M.D.

Director, National Institutes of Health

Thank you, Dr. Kupfer. It is a pleasure to welcome all of you to the National Institutes of Health. I am particularly interested in the proceedings today, because the conduct of clinical trials is a cause in which I strongly believe. We cannot afford the luxury--if indeed we ever could--of supporting only research. As ardently as I believe we must pursue research at its most fundamental level, I am similarly convinced that we must simultaneously figure out how to spread the fruits of that research to the clinical practice of medicine. Our commitment to the practical application of research results, a function which we call knowledge transfer, is something we talk a lot about these days. For how can we expect the American people and their elected representatives to continue supporting scientific research if we cannot point to some examples of how that research has benefitted mankind?

As it happens, the National Eye Institute has provided us with one of the best examples of how the results of clinical research can be used to improve the quality of life for a large number of people. I am speaking of the Diabetic Retinopathy Study. After years of uncertainty over the value of lasers in treating diabetic retinopathy, the NEI tackled this controversial issue. In the face of criticism from the ophthalmological community, the NEI launched a nationwide, multicenter clinical trial of photocoagulation for people in

* Meeting to obtain new data on radial keratotomy, June 11, 1981

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advanced stages of diabetic retinopathy. The Diabetic Retinopathy Study showed that photocoagulation could reduce the risk of severe visual loss by 60 percent in patients with advanced diabetic retinopathy. This discovery has made it possible for ophthalmologists to offer a highly effective treatment to the 300,000 Americans who are now at high risk of diabetic blindness. It has been estimated that this photocoagulation treatment may eventually save the taxpayers as much as \$4.4 billion dollars. This is a benefit that far outweighs the \$11 million spent for the study. Of course, not every study will yield such a high return on our investment of the taxpayer's dollars. But it is certainly a goal to which we aspire.

In order to support such fine quality research, the National Institutes of Health must set rigid standards for review of research proposals. When a grant application is submitted, it is assigned to a study section which reviews the study protocol for scientific merit. Then an application for NEI support is reviewed for its relevance to the program goals of the NEI. (The NEI is a leader, I might add, in program planning to achieve the maximum amount of quality research with a minimum of wasted dollars.) Then, if the grant is approved, it can be funded.

It is my understanding that a grant application submitted to the NIH for a clinical trial of radial keratotomy went through the peer review proceeding I have just described. Since the time that review took place, it is possible for new information to become available that would cast doubt on the need to carry out plans for such a study. It also is my understanding that some pioneers in

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the development and refinement of radial keratotomy do indeed contend that information on the safety and efficacy of radial keratotomy is now available. Since I fully share Dr. Kupfer's concern about unnecessary Government spending, I am eager to hear what data you have to present today. Like Carl, I can't imagine NIH supporting a study to collect information that already exists. We have, therefore, gathered here today, so that you have an opportunity to prove your claim that the data sought by the NEI-supported study of radial keratotomy is already available. Ladies and gentlemen, we are listening.

"TOMORROW'S MEDICINE"*

by

Donald S. Fredrickson, M.D.**

I have been asked to practice shuttle diplomacy and to arrange a moratorium to cool off a serious confrontation between Houston and Washington.

Admittedly, your Vice Chancellor for Health, Ed Brandt, who is now my boss, was drafted from the University of Texas and brought to Washington to head the Public Health Service as Assistant Secretary for Health. And granted, Vice President Bush was recruited from Houston -- but do you think it was fair for the Houston Rockets to steal Elvin Hayes from the Washington Bullets?

I am authorized to seek a truce.

* Commencement address, University of Texas Medical School at Houston, June 13, 1981.

** Director, National Institutes of Health, Bethesda, Maryland.

Editorial note: Similar comments under same title were presented at the commencement of Georgetown University School of Medicine, 5/30/81.

While you've been thinking "It's all over today!" I have been thinking about your education tomorrow.

When I was on the housestaff in Boston, the dean of the Harvard Medical School was Dr. C. Sidney Burwell.

At commencement one year, Burwell told the medical graduates that half of what they had been taught by the faculty was wrong. The problem, he said, was that he didn't know which half.1/

Nowadays it's no easier to tell. The heart sounds are probably here to stay, but not much else. There's never been a period like this before, with the knowledge base in medicine melting down as rapidly as it forms -- and just when it has become so expensive to acquire it.

For molecular biologists, the current falling into place of countless, long-scattered details of living systems is a "revolution." For physicians, charged with understanding the sum of the parts, these times reek of anarchy, and with the threat of early obsolescence from so much rapid change.

Cheer up, from my perch, with its view of tomorrow's medicine, I have seen help coming. I think your class may be among the first to grasp the means of navigating the rising torrent of new information.

Quite recently I sought the answer to a question at the National Library of Medicine, on the campus of the National Institutes of Health. Here is the very center of the network of communications which links the world's laboratories for biomedical research. Entering the door I was reassured by the sight of the obligatory spiral of DNA hanging from the ceiling in its accustomed place.

Below it, however, my gaze met an unfamiliar void. Some seismic event had covered up the catalog of a million cards! Amid the emptiness sits a small computer terminal beckoning one to converse privately and directly with the Delphic source.

A data-handling revolution has finally overtaken the biological one. The flood of information has been tamed in the nick of time.

In the coming years, you will have your personal computer in practice: first, as a memory-extender, knitting the threads of information from the patients in your practice into a greater fabric of similar experiences woven from medical practices far removed from yours in time and space; second, as a "consultant," bringing the consensus of many experts to help you interpret the changing array of clinical and laboratory data; third, as a prognosticator, laying out probabilities for the case before you; and finally, as a guide, carrying you through the ever-expanding algorithms to the endless decisions on treatment and prevention you will have to make.

Medical students and practitioners in the Houston area have many unique resources and advantages because of the concentration here of academic institutions, professional schools, hospitals and most of all a community's commitment to their excellence. One

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outstanding example of what can be done in such an environment is the development of the Texas Medical Center/Houston Academy of Medicine Library. In being only five years, this jointly supported facility is either the primary or secondary library for perhaps more students, faculty members, researchers and health practitioners than any other medical school library in the United States. The concept of the library is typically Texan -- big, practical, and original.

Inclusion of the Harris County Medical Society Headquarters in the Jones Library Building is more than symbolic of the unbroken continuum -- the lifetime studenthood of the medical practitioner.

Because of the revolution in communications, the meaning of commencement exercises like this is changing. Once it was traditional for medical graduates to cleave into unequal parts: the great majority to go off and practice today's medicine, a small academic

minority remaining behind to weave the medicine of tomorrow. These two populations of doctors have traditionally worked apart with only one-way communication. Now, with more and more practitioners "on line," to the source, that gap among doctors is going to close. A compression of our countless individual experiences into a single, better-shared medical universe is inherent in the twin revolutions in biology and communications that envelop us.

I belong to something called the Peripatetic Club. It's a small club of professors, an "anachronism" of communication, conceived in Osler's time to keep the academic centers of the American Northeast in intellectual parity. Nowadays we have it to keep up with the University of California and University of Texas systems. Recently our meeting was at Johns Hopkins. Somebody was talking about closed-chest cardiac massage. Could there really be anything new, I

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wondered, on the subject of cardiopulmonary resuscitation? I was leaning sleepily on Resusci-Anne,[®] the CPR dummy. Suddenly, I swear she took a tremendous breath and blew over a durable old hypothesis.

The mouth-breathing part of CPR is as old as the Book of Kings II, where Elisha's story of reviving a child by this method appears briefly. More than 20 years have passed since Kouwenhoven and Knickerbocker made us all conscious of closed-chest cardiac massage, the rhythmic squeezing of a stilled heart between the sternum and the spine to make it pump blood again. Any physician, every conscientious paramedic, all the nurses can tell you how it works. Now suddenly we discover that the explanation is wrong!

The heart, it seems, cannot be made to beat mechanically by pushing it or squeezing it from without. "Cardiac massage," it turns out, is really artificial respiration. Blood is moved to the periphery

because of changes in intrathoracic pressure. Rhythmic pressure differences become the "pump," and the valves in the peripheral veins, rather than those in the heart, serve to maintain artificial circulation.

This overturning of conventional (nay, classical -- Harveian) dogma has a symbolic significance for all medical students in any generation. It reminds us that we will never comprehend living systems without ceaseless refinement and reordering to explain the anomalies that are seen by those whose eyes are open.

You will leave here today, then, as physician-scientists, linked to one another through ever-accumulating data banks and equipped with skills subject to a lifetime of continual correction. You have joined a profession engaged in a dynamic quest for deeper understanding of life. Membership gives you advantages of knowledge not offered to all citizens. This entails certain responsibilities.

One is to unite in fostering and protecting the continuous expansion of knowledge and the relentless reduction of ignorance about nature and ourselves.

There can be no forbidden knowledge about life, provided we devote equal attention to wise and just uses for all we learn.

As physician-citizens we have additional responsibility to cultivate in our society a balanced search for knowledge. A fascination with new powers for reduction of life to molecular terms must be matched by zeal to resynthesize, for useful and humane purposes, the pieces so brilliantly exposed.

There is a practical side to this need for balance:

The nutritional sciences, for example, can be permitted long excursions in the disguise of biochemistry or biophysics -- provided they return now and then to tell us what we ought to eat.

There is also a moral side to the need for balance:

Does, for example, the excellent care we now can provide for the victims excuse our still inadequate efforts to understand the origins of violence?

Finally, don't be discouraged or misled by this promise of restless change in the scientific content of medicine. Do not mistake my deliberate emphasis upon objectivity. Remember your individuality -- and that of each of your patients -- will keep alive the art in our calling. The beauty of the new technology is the power it has to give us extra time for understanding the patient less in isolation and more in the context of his culture.

Increasing understanding of how one person's health and illness relate to all the others persons affected by his life will lead, in turn, to strengthening of the fragile and still imperfect social institutions -- families, cities, and an uneasy world -- of which all of us are part.

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I have spoken of the lively base of medical knowledge and the current revolution in communications. It is obvious that these realities will demand more, rather than less, of each of you in terms of commitment and compassion. For what we do -- for our own sakes as well as for the sake of those we serve -- demands more than our minds, no matter how well-trained or often reinforced. It asks for soul.

William Butler Yeats in his petition for poets could just as well have been phrasing the doctors' prayer:

"God guard me from those thoughts men think
In the mind alone;
He that sings a lasting song
Thinks in the marrow-bone."

1/ Burwell, C.S.: in Beecher, H.K. and Altschule, M.D.,
Medicine at Harvard. The First Three Hundred Years.
Hanover, N.H., Universities Press of New England. 211, 1977.

REMARKS TO THE NIH COMMUNITY*

by

Donald S. Fredrickson, M.D.**

Today, I wish to speak of several matters of importance to NIH.

First, I want to assure you that NIH is healthy, strong and in the prime of its life.

The second is to announce that Ed Rall will serve as Acting Deputy Director for Science beginning July 1. I am also pleased to announce that John Eberhart, who is retiring as Scientific Director of Mental Health, will also be coming to Building One as Special Assistant to the Deputy Director for Science.

This aggregation of great strength suggests the dimensions of the loss that all NIH and I, personally, feel at the departure of Bob Goldberger to be Vice President for Health Sciences and Professor of Biochemistry at Columbia University. Bob succeeded Hans Stetten as Scientific Director unofficially in September 1979. As many of you remember, his selection resulted from a highly unusual canvassing of opinions from intramural scientists during which I consumed nearly 80 cups of tea and coffee.

In seeking your participation in finding new leadership for the NIH Intramural Program, I sent each of the senior scientists a letter reminding you of our need to preserve "an unprecedented capability for research in the life sciences that is represented by NIH laboratories and clinics." And that even though "the human and physical capital of the intramural program is awesome and its power for continued accomplishment seems unlimited . . . the essence of its greatness is fragile and could be quickly destroyed by careless trustees."

When I selected Bob Goldberger, I gave only one piece of advice. It is a saying of Alfred North Whitehead's that has always summed up for me the administration of a complex, organic institution like NIH, set down in a politically oriented cosmos. It is that "Style is the ultimate morality."

* Presented in the Masur Auditorium of the Clinical Center on Friday, June 19, 1981.

** Director, National Institutes of Health, Bethesda, Maryland.

Bob has shown a style of his own which now also reflects the polishing expected from instructive contacts with those grinding stones, the Scientific Directors. I believe the changes which he has introduced in the processes for determining tenure and for more uniform review of scientific performances were overdue and most important in sustaining the insistence upon excellence required for justification of these precious resources. To Bob and to Dr. Kathleen Mullinix, who will leave with him, and to Philip Chen, who fortunately remains, I extend my thanks — and yours.

I also wish to recognize the dedicated contributions of Ted Becker, appointed Associate Director for Research Services in a reorganization begun in 1979. This new office has been an essential step in enabling us to begin crucial determinations within the next several years of the conditions under which an intramural program, which has ceased to expand, must sustain its excellence. We must decide upon the appropriate ratio of scientists to staff and the reallocations of laboratories and beds required for optimum vigor of programs dependent upon a proper balance between the young and the more experienced. The new Division of Safety, which takes advantage of the gifts of Emmett Barkley, provides a long-needed coordination of the activities destined to protect our scientists and to help other institutions do the same.

NIH seeks to modernize its older laboratories; the six oldest buildings — 2, 3, 4, 6, 7, 8 and 9. This will require on the order of \$50 million in capital expenditures and years of round-robin moves to complete. It will mean inconvenience, too; but to neglect the fading conditions of these venerable quarters is to tolerate imminent hazard to our colleagues.

Rising invisibly behind us as we sit in Masur Auditorium this morning is the greatest single renovation project in NIH history. The ACRF will be dedicated in October of this year, and fully occupied within 2 more years. Its construction permits a hospital, designed in 1948 and grown incapable of modern care, to be "born-again," equipped for service into the 21st century and with the greatly expanded capacity for outpatients that reflects the future of biomedical research.

ACRF is more than a renovation. To me its young structure already is a repository of memories . . . the afternoon when I was allowed just 20 minutes to convince then Secretary Weinberger to put the necessary \$105 million back in the budget . . . the formation of the planning committee under Ed Rall . . . the approval secured from the BIDs to use operating funds for construction, if need be . . . the

decision to build a glass tower . . . the latter-day effort of all of us to secure the needed additional funds for modernization of the Clinical Center to effect the harmonious integration of these two structures.

ACRF is an innovation. I envision it as representing a new Bauhaus in the kind of multidisciplinary attention to complex problems in free populations that the Clinical Center represented in its time, in reference to intensive in-patient research. Here is the retort in which the pieces so brilliantly exposed in the biologic revolution can be resynthesized. It is the laboratory in which a more "humanistic biology," so often demanded by critics of intensive reductionism, can be created and tested.

To realize the full potential of the ACRF is going to be one of the greatest challenges for the NIH of tomorrow.

Next Thursday, Secretary Richard Schweiker of Health and Human Services will make his first official visit to the NIH campus.

This Secretary has the most extensive background in NIH and biomedical research of any in the history of the Department or its predecessor. (As I wrote him this week) . . . "I very much appreciated (his) immediate invitation to continue in my post upon his taking the office as Secretary" and ". . . our personal relationship has been one of mutual interest and respect . . ."

His itinerary will begin in Building 1. From there, we will show the Secretary and his party NLM, DCRT, the ACRF, and Buildings 2 and 7. His visit will allow a number of you to discuss your scientific work with him. In consideration of his high interest in research leading to primary prevention, the Institute Directors are going to serve him from a luncheon menu of major prevention initiatives. This will include some intramural as well as external components. He will spend all day here on Thursday, the 25th.

Secretary Schweiker will be the fifth Secretary I have introduced to NIH in the role of Director during the past 6 years. In that time, far more than the ACRF and the Lister Hill Center has been constructed.

All human biology has been in a rapid state of transition during that period and every institution involved with the life sciences has felt the perturbations. Here we are the center of the world in human biology — a position claimed both from the unparalleled capacity of this campus for research and by the magnitude of

resources for extramural support that are under our stewardship. Thus we have been a center of that transformation. A few of the landmarks particularly stand out:

- The implementation, immediately after Asilomar, of the first restrictive code for biological research . . . a responsibility to balance the scientific imperatives against the public interest, an interface fragmented by a wide range of anxieties and special interests . . . the achievement of new processes without restrictive law, an example extending to laboratories in all advanced countries throughout the world. Looking back, I think we can say: "NIH managed well."
- In 1975, one of the most prominent defects to be repaired at the boundary between NIH and society was the definition of the proper limits of the boundaries themselves. More specifically expressed, our task was to determine how to protect our scientific programs from regulatory and service obligations, including excessive health promotion activities while remaining sensitive to criticism directed to science for rising costs of health care and a proliferation of new technologies. There were serious threats that in responding we might needlessly harm the objectivity of the search and fail to maintain the sharpness of the instruments of scientific inquiry.

Some answers were found to how we might demonstrate properly that science was not uninterested in the obligations created by the technology it spawned. From this campus came the concept of Technical Consensus Exercises . . . which have caught the imagination of health scientists, providers, and the public abroad as well as in this country. I regard, too, the increasing quality of clinical trials and a sharper definition of ethical procedures in human investigation as also among the accomplishments which have granted us successful passage through the difficult and highly critical mid-seventies.

- The impact of economic change began to be felt in the late seventies . . . a cooling down of capacity to fuel the vast system for inquiry as the biologic revolution heated up. Changes were demanded in laying out the macroeconomics of research resource allocations (SATT), coordination of programs extending over the borders of single categorical institutes ("trans-NIH activities"), formation of the National Toxicology Program, the laying

of strategies for funding (principles) and for stabilization of support in the highly complex and fluid dramatics of Administration budgets and Congressional authorizations and appropriations, and now, the preparation for the zero-sum game of allocation between sectors of research. The "5,000 new and competing grants" is a chapter yet to be written in the history of maturation of both NIH as a community and the federal government as patron of science. I'm convinced we were correct in our strategy.

Behind the continued scientific success in both the intramural and extramural worlds, then, there rises a backdrop of major mountains created by administrative exertions over the last few years: Recombinant DNA Guidelines, ACRF, Consensus and Transfer, Health Research Planning, Stabilization and the 5,000 grants, and more recent labors with the Institutional Support of Research, Patents, Commercial Interfaces, Indirect Costs and Excessive Accounting.

There were other ecumenical tours de force, too (like the Interagency Radiation Research Committee, to name but one), but they involve too selective a participation to mention in detail here.

Future: I think the optimism so essential for success in science is an indelible as ever. The future, however, will require more of us than the past:

- Sufficient flexibility, while sustaining the best traditions, is going to be needed to adapt to funding that will be level at best, possibly with modest compression, as increases fail to meet inflation demands. I have already made reference to adjustments of balances in the Intramural Program, which must share the general fortunes of the Extramural World.
- The next decade is going to test the institutes as never before in terms of other corporate responsibilities.
- To begin with aggregate budget distributions as a basis for strategy — not to end with them. Planning that declines to a mere summation of competitive, independent categorical programs is not foresight.

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- To select priorities for the funding of research by the different mechanisms of the present and possibly new ones for the future.
 - Especially, to keep up creativity in continuous adjustment of the balance between categorical objectives and the provision of communal resources to maintain the strength of the institutions in which the majority of scientists work and teach.
- Attention to the style and substance of activities, other than experimental work, by which NIH also merits high rating as a social institution:
- continued provision of technical consensus and objective evaluation of technologies;
 - education for both providers and recipients of health care so that change in scientific knowledge can beneficially affect their lives and practices;
 - faithful curatorship of invaluable collections of data, and the tangible collections of objects (cell lines, mutants, etc.) which join us to proceeding generations and they to the future;
 - rigorous defense of scientific ethic and scientific freedom, for they are inseparable.

At NIH, the endless cycle of renewal must begin again — it is the nature of the place: This summer, in addition to Bob Goldberger, Institute-Director chairs must be re-filled: that of Donald Tower in Neurology and Bob Levy in NHLBI. They will be missed — but they, and any others who go, will be replaced to maintain the tides.

This July, I am completing my fourth seven-year term at NIH. It seems as exhilarating and worthwhile as in the summer of 1953, when I arrived. On such a large stage, however, continuous appearances may lead to changing quality of performance. At least it narrows the perception of reality.

My last six years have been spent in the relentless company of the administrative burdens of the Director. It is time to shed them for a while, lest I forget completely how to be a scientist and a physician.

Therefore, I have yesterday sent to the President a letter containing these sentences:

Dear Mr. President,

I respectfully request that on the first day of July you accept my resignation as Director of the National Institutes of Health. It is for personal reasons that I take leave of this position, which I have been honored to hold these past six years. Before then, I was also privileged to spend much of my scientific career at the National Institutes of Health.

I am most grateful for the continuing trust which you and Presidents Ford and Carter have extended in allowing me to lead this remarkable institution.

With my best wishes for your personal well-being, and the continued success of your Administration, I remain

Sincerely,

This is not the easiest time I have appeared before you.

I want to thank everyone here. Especially several faces in the front row: Virginia Tilley Ono, my first secretary at NIH; Margaret Quinlan, my expert word processor; Nancy Hawes, arbiter of syntax; and Bel Ceja, housemother of all NIH.

For Miss Poes, who came with me here in the hot summer of 1953, and has made the long stay possible, I reserve my deepest thanks.

I want to thank all of you for making me Director. As Director-Emeritus I hope you love and respect me just the same.

New Structure, New Paradigm*

DONALD S. FREDRICKSON

Thesis: This is a most important phase in the history of the NIH Intramural Research Program, one of the largest, most productive and oldest of the institutions for biomedical and behavioral research in the United States. Intramural NIH is a master-link in the worldwide chain of universities, independent laboratories, health practitioners, hospitals, and allied industries dedicated to a universal human purpose. The Ambulatory Care Research Facility (ACRF) is more than a hospital renovation or new structure. It symbolizes a new phase in biomedical research that must inevitably follow the waves of enlightenment occurring in cellular and molecular biology. The same energy and creativity spent in these reductionist activities, which have been so profitable and exciting, must be dedicated to integration and resynthesis of knowledge of man. The opening of the Clinical Center nearly 30 years ago provided great expansion of intensive clinical investigation, leading the way into the age of *molecular diseases*. Now the opening of the ACRF can set a paradigm for multidisciplinary studies of the development and adaptation of each genetically unique individual to his environment and culture. It does not matter whether this emerges as *holistic medicine*, *humanistic biology*, or *sociobiology*, as long as it advances the understanding of ourselves and our societies in a scientific and steadfastly humane setting.

On an occasion such as this, one should stress clinical investigation—that difficult hybrid of science and the arts. It will not be necessary for me, however, to display credentials of support for basic, fundamental, and nonclinical research as representing part of the milieu of the finest clinical investigation. This credo is symbolized by the location of the Clinical Center *within* the whole of the NIH Intramural Program and its extramural counterparts in basic science.

The NIH is a very old part of biomedical science in America. The direct progenitor of NIH, the Hygienic Laboratory, was opened in 1887. This was not very long after the Bowditch Laboratory, considered the first American laboratory in the basic sciences, had opened at the old Harvard Medical Building on North Grove Street in Boston (1871). Johns Hopkins University was opened in 1876, as the first university emphasizing the importance of research in university teaching. It was the successful example of Hopkins which later inspired Abraham Flexner to broker the lasting marriage between science and medical teaching in the USA.

During the time of the rise of the Rockefeller Institute as the first American medical research

institute (1910), and the establishment of the clinical research unit at Hopkins Medical School, a model preceding any in Europe, the Hygienic Laboratory moved to Washington. Its staff participated in solving problems of infectious disease and nutrition in the practical ways for which federal support for science had been harnessed from the beginning of the republic.

In the past few months, I have had a modest amount of leisure to study the evolution of the federal support of science. Primarily, I have done so to seek some revelations in that history that will tell us how the federal system may adjust itself or be rationalized in the wake of a sudden chilling of the economy supporting it. There are reminders in that history of the importance of a few key individuals in the developments leading to America's emergence as the leading scientific power in this century. One of those people is Warren G. Magnuson who is being honored by becoming a permanent part of the name of the Clinical Center. All of us will remember him for his work in the Congress to keep bright the lamp illuminating the search for new fundamental knowledge while never neglecting an interest in seeing that this knowledge was turned into applications for betterment of man's condition.

Senator Magnuson exemplifies a quality that is vital to public support of institutions which cannot promise early return on the investment made in them. Throughout American history, certainly since the Administration of John

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*Editorial note: This article is included here (although prepared after Dr. Fredrickson left NIH) because it contains valuable background on events occurring between 1975 and 1981.

Quincy Adams, the Congress has played the dominant role in determining how public funds will support science in America. It is most encouraging that within any Congress there are always a few persons who have both the spirit of the Enlightenment and a practical bent for harnessing the political process to further its ideals. The effective support of science in the fulfillment of the mandates of the Constitution involves an understanding that basic knowledge is required *before* technology can be created to chart the harbors, grow and harvest better crops, assure a proper defense, or protect the health of the people.

Through its long legislative record, the Congress has thus repeatedly underscored its support for use of public funds for basic research. The institutions it has created, particularly during the latter half of this century, to carry out this sensible interpretation of the powers given to the federal government, represent essential political contributions to the present biological revolution.

The history of the transformation of the Hygienic Laboratory to the present NIH is too complicated to retrace in its entirety. However, Senator Joseph Ransdell of Louisiana, who brought about this early conversion of a service laboratory to a research institute by his dedicated labors in the period 1926-1930, must be mentioned. The further multiplication of the first National Institute of Health into the many Institutes which have promoted scientific discovery and achievement since 1937 is due in no small part to the support of Senator Magnuson. He was not only a key supporter of the growth phase of NIH but also of the formation of the National Science Foundation in 1946-1950. One cannot follow the path of the science agencies through Congress without recognizing a special quality in the relationship between biomedical research and the American people, as represented by Congress.

Let me concentrate on events surrounding 1953 and beyond 1981. On the first of these two dates the Clinical Center opened. There is a *Bauhaus* dimension to the impact of the Clinical Center upon clinical investigation in America and in the rest of the world. It was at first an impact of scale. None of us who came as physicians to share in the opening had experienced the depth of exposure to science—in a medical milieu—which this campus offered. From the size of the Intramural program there

quickly arose derivative advantages that enhanced the uniqueness of such a place: unlimited collaboration, freedom from distractions of service and teaching, all the expertise and facilities necessary to convert almost any good idea into an experiment, and the constant stimulation of exposure to a high intensity field of optimistic curiosity. Two wars, with their attendant doctor drafts, undoubtedly helped bring so many of the brightest to Bethesda. On the other hand, the numbers of scientifically trained physicians who returned to university faculties provided for continuity in the quality of medical education available across the land. Even now, as one goes to universities throughout the country, the several generations of alumnae are everywhere visible, setting standards that help maintain the quality of their institutions.

Overseas, NIH Intramural is regarded as both a vital collaborator and a formidable competitor by colleagues in the developed nations, and as an ideal by scientists from less affluent cultures. It is a world standard that is maintained in this house. Because NIH has a wonderful environment to offer scientists, it also has very large responsibilities.

Having played some role in the establishment of this new research facility while the Director of NIH, I still feel a strong sense of responsibility to see it properly launched. In considering its purposes, I have always thought of the ACRF in two parts, one above the other.

The lower part represents an essential renewal of the Clinical Center. The new and once unique appointments of the main Hospital had been reduced to obsolescence by the very forces of change it had done so much to set in motion. I will not dwell here upon my memories of the quest for support for renovation: the guided tours of gowned and masked Congressional delegations through outmoded nooks and crannies and memorable discussions with Secretaries (past) about hospitals (future) and budgets (present). The new building and the modernization of the old one, now so far along, will fit the Clinical Center for leadership well into the next century. This is a timely renewal, for what can be done in the Clinical Center is not becoming easier to do in many other centers for clinical investigation around the country. As the extramural resources become more constrained, the Clinical Center begins to move back toward its earlier, more unique status. Continued effective

use of the great capacities of the facility is a trust held by NIH, and by its federal overseers.

The second part of ACRF represents another responsibility and a great boon for both NIH and the nation. I am not speaking simply about new clinic space on the upper floors and the expanded capacity for outpatient visits. I am speaking about the opportunity for this new addition to give shape to the newest paradigm of clinical investigation. We have already reached a stage where the importance of ambulatory research is recognized. What we have not reached is a clear expression of the future possibilities for scientific study of adaptation of individuals to their environment and culture.

Some time ago, I went to participate in a program in Philadelphia called "Saturday at the Museum." My companion on the platform was Professor Rene Dubos. Professor Dubos, who calls himself a despairing optimist, is both a leader in biomedical science and one of its major critics. For many years, he has expressed impatience with the degree to which the holistic in biology and medicine seems to be at the mercy of the reductionist. He deplores a belief shared by some scientists that the only fields of biology deserving to be called fundamental are those that deal with the simplest manifestations of life. He argues that such a limited approach is insufficient to create a science of life, let alone of man. What one needs, says Dubos, is a *humanistic biology*.

I have come, over the years, to be increasingly sympathetic to Dubos' point of view. Not because I deplore reductionist research, but because I fear we have no time to waste in achieving a organismic reconstruction from the new cellular biology to better our understanding of the complete man and his societies.

Given the speed of innovation today, and the accelerated demand for wisdom, it is inevitable and desirable that biomedical research will be steadily transformed. It will move in the direction of continuing synthesis of the molecular with the experiential, on an ever larger scale, for the purpose of removing obstacles to the realization of human potential.

During the decade ahead, the fragile border between the social and the natural sciences must be tended carefully, so that what is now a nervous entente will steadily be converted to a single stable community. New techniques, which will be primarily but not exclusively statistical ones, will increasingly provide opportunity for

experiments integrating the disparate sciences.

I believe Dubos is correct in suggesting that present research institutions will move increasingly away from "highly individualized" (project) organization structure to "highly organized long-range programs." I do not believe they will reach his ultimate imaginings of some "collective form of intellectual life...akin to medieval monastic orders." Some of the Cartesian exclusiveness always will elude confinement in the Baconian commune. However, a less insular and more exciting arrangement now may rise in Bethesda. The ACRF symbolizes the increasing concern with prevention and ambulatory health care. It shifts the emphasis from the *intensive* study of the inpatient detached from his world to the *extensive* observation of people who continue in full contact with their usual physical and cultural environments.

What I, too, dream this will mean is a rise of multidisciplinary clinics in which the behavioral, anthropological, and other social sciences, the natural sciences, and the medical, dental, and nursing professions will come together to master complex disorders. What we must hope to create here are newer paradigms for understanding of the dyslexias and other disorders of learning; of the minimal disabilities in communication which impair social adaptation; of the behavioral and affective abnormalities having both intrinsic and extrinsic determinants; of the nature of dependence upon tobacco and similar other destructive habits; and of the many other problems of people for which creative application of the methods from several disciplines can combine to achieve insight and relief that purely molecular views may not.

Such integration will take time. It will also take continued support and administration skilled in creating possibilities in times of austerity. Above all, it will take gifted physicians, scientists, and all the other dedicated kinds of people who need to be along to make such a venture successful.

Once I used to say, at least half in jest that, "As Archbishop of the Diocese of NIH, I am endlessly being called here and there to consecrate ambition." I don't know if a retired bishop loses his sanctity all at once or whether it takes a season or two to ooze away. In case it's the latter, I'll pound on the floor with my rented crozier a few more times. I do want this dream to come true.

rDNA CONTROVERSY:

THE NIH VIEWPOINT

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Revelation from human history takes time. And, as the gospels have shown us, both strong belief and opportunity to work it out as a community also are helpful. This symposium serves to help us weigh what we respectively believed and did during "the rDNA controversy," and judge the appropriateness of these actions with hindsight. A second purpose, of course--and somewhat more important--is to consider not so much the past as what we are to do in the future. This includes the future use of rDNA technology as well as the manner in which we should handle other controversies of a similar kind.

It is my assignment to cast reflections from the many-surfaced mirror of the federal government. What did it do? What did it seem to do right and why?

In the space available to me, I would like to state my views (the italics are mine) of some things the government did right and where it might have gone wrong. Of course, I will have some biases. This will be the first occasion since leaving the NIH directorship that I have had opportunity to expand upon them.

*Editorial note: This paper will appear in a 1982 publication of the American Association for the Advancement of Science. It is included here (although prepared after Dr. Fredrickson left NIH) because it contains valuable background on events occurring between 1975 and 1981.

NIH AS LEAD AGENCY

In my opinion, one of the good moves of the federal government was that it let the National Institutes of Health (NIH) carry the principal responsibility.

In 1977, one famous scientist wrote, "I consider it a true calamity that the agency dispensing nearly all the federal funds available for biological and biochemical research, NIH, has become a party in the debate...."^{1/} Elsewhere, he opined, "...the National Institutes of Health have permitted themselves to be dragged into a controversy with which they should not have had anything to do," and, "...our time is cursed with the necessity for feeble men, masquerading as experts, to make enormously far-reaching decisions...."^{2/}

Another critic wrote in the same period, "...an ethical conflict of interest arises when it [NIH] is entrusted to set up guidelines to regulate the very research it is committed to promoting...."^{3/}

I agree with the appearance of a conflict of interest. It was unavoidable. It was bothersome all the way. One of the most important lessons to be learned about controversy over use of high technologies, however, is the absolute requirement for expert opinion. The most informed experts will very often include those using or promoting the technology and there will be an appearance of conflict of interest. The art of solving this kind of problem lies in the manner in which one joins the experts with the other parties at interest.

The NIH had at least six distinct advantages which made it as the agency of choice for assumption of the major responsibilities in establishing guidelines and providing the focus for federal activities concerning recombinant DNA.

- NIH had originally been asked by the scientists involved to help. In an often-cited letter to Science of June 26, 1974, to the Director of NIH, eleven scientists acting for the Assembly of Life Sciences of the National Research Council and representing some of the key molecular biologists attending the Asilomar Conference, requested NIH to start a program to evaluate the biological and ecological hazards, to consider procedures to minimize the spread of recombinant molecules, and to devise guidelines for investigators.^{4/} NIH therefore had the confidence of the scientific community most directly involved.
- NIH was funding far more of the research involving recombinant DNA technology than was supported by any other source. It therefore had the clout to use sanctions available to enforce adherence to guidelines if this became necessary.
- As a federal agency, NIH was controllable by the whole structure of government, including federal law; all the checks and balances of the system were in place; and most came into play as the debate became increasingly adversarial.

- Among all federal science agencies NIH has a unique feature whose essentiality in such a controversy was not immediately recognized. This feature is the great size and quality of its intramural research program. The presence on the NIH campus of many experts in the techniques in question--scientific peers of those in the extramural community--made it possible for NIH to weather the storms blown up around the speculative hazards and the threats to scientific inquiry inherent in the crisis. From among the staff I quickly assembled the NIH "Kitchen-RAC," which counseled and crafted solutions to endless problems as this complex and lengthy transaction proceeded. As Director, I spent a third to half of my time on recombinant DNA in 1976 through 1978. This was but a small fraction of the total NIH person-hour expenditure. I would have wasted those hours of mine, but for the dedicated and talented scientific and administrative NIH people always at hand. Praise of these persons is one of the neglected choruses in the rDNA epic.

The daily menu for the "Kitchen-RAC" (named after the parent NIH Recombinant Advisory Committee) was usually prepared by Joseph Perpich, associate director for program planning and evaluation, and Bernard Talbot, special assistant for intramural affairs. Perpich's combined medical and law degrees, plus a clerkship with Judge Bazelon and time on the staff of Senator Kennedy, enabled him to provide me with invaluable advice on meeting both legal responsibilities and political objectives. His specialty training in psychiatry also came in handy. Both an M.D. and a Ph.D., Talbot was the perfect antidote for perjorative

views on productivity of government employees. His Stakhanovite work habits enabled him to produce mighty drafts and redrafts of revisions of the highly technical guidelines in response to endless commentary and pressure for alterations. Other invaluable contributors were Emmett Barkley, director of the office of research safety; William Carrigan, the editor of the NIH papers on recombinant DNA; William Gartland, director of the office of recombinant DNA affairs at NIH; Susan Gottesman, a scientist in the laboratory of molecular biology in the National Cancer Institute, and a member of the NIH Recombinant Advisory Committee; Joseph Hernandez, an attorney and member of our division of legislative analysis; Malcolm Martin, a virologist and molecular biologist from the National Institute of Allergy and Infectious Diseases (NIAID), Richard J. Riseberg, NIH's legal advisor, whom I once called "a double agent with cover blown from the start," because he was officially in the HEW General Counsel's office; Wallace Rowe, a famous virologist member of the RAC, and laboratory chief at NIAID; Betty Shelton, whose staff had a prodigious capacity for production of copy; and Maxine Singer, a Cancer Institute molecular biologist who had been in on the rDNA controversy from the start, and whose contributions toward its resolution were both legion and indispensable. Burke Zimmerman, who joined us later on, brought with him the valuable perspectives of the environmental groups and of the Congressional staffs.

-6-

- The most important advantage of NIH was that it was "there"—staffed, integrated into government, and ready to go. The rDNA controversy needed to be dealt with "on-line" and within the existing framework of government. It can be a grievous error to assume that dilemmas involving profound questions about science should automatically require new, untested forms of solution. In the first three to four years of the controversy, it would have meant chaos to have handed this problem to some part-time commission made up of busy citizens, no matter how distinguished.
- NIH was a science agency without formal regulatory experience or authority. Had it been an agency that was so endowed, such as the Food and Drug Administration (FDA), the Center for Disease Control (CDC), or the Environmental Protection Agency (EPA), it could not have kept the setting of standards and their revision out of the chilling grip of conventional regulation. This would have involved the tedious, stepwise processes specified under the Federal Administrative Procedures Act (FAPA). Every decision arising from the stream of new knowledge would have to be diverted into the Federal Register for publication and comment. The risk of slowing the evaluation of the science into a sludge of unfinished experiments and unsatisfied hypotheses was too great. Rather, with the concurrence of superiors in the Department, I decided we should take advantage of the previously established practice of NIH Directors to impose certain conditions upon scientists as guidelines. To this we would add

the specifications of the Federal Advisory Committee Act (FACA), protecting public access to the decision-making process. We would refrain from the formal Notice of Proposed Rulemaking which would have placed us in lock-step with the regulatory process. To be sure, well-informed critics like Peter Hutt took the NIH to task for its unseemly amateur performance as a regulator,^{5/} but we were determined to walk the narrow edge of the abyss until a special procedure for evolving the guidelines, consonant with the pace and scale required to synchronize experiments in scores of laboratories, could be established. As it turned out, this took two years of departmental negotiations and public hearings to establish.^{6/}

ECUMENICAL EXECUTIVE AGENCIES

Once harnessed, all the government executive agencies, research and regulatory, worked harmoniously.

In the beginning, there were at least four government agencies supporting recombinant DNA research (National Science Foundation, Department of Agriculture, Veterans Administration, in addition to NIH). These agencies, it quickly became apparent, would need to agree upon a single set of standards. Moreover, there were a half-dozen, including FDA, EPA, CDC, the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), and the Federal Transportation Agency (FTA), which believed their authorities permitted them some regulatory authority over the products of such research, perhaps even the laboratory experiments. As soon as we had

guidelines ready for promulgation, I obtained the agreement of then Secretary Mathews of HEW to urge President Ford to convene an interagency committee, to include all of the above, and other federal agencies, like the Council on Environmental Quality (CEQ), the Departments of Justice, Defense, and Commerce, and the Office of Science and Technology. Months went by with no issuance of a Presidential order. Finally, Senators Kennedy and Javits issued an open letter demanding such action, and the committee, which I chaired, got down to business in November 1976. Fairly quickly it achieved three objectives:

- The research agencies (despite some sacrifice in autonomy) agreed voluntarily to adhere to one set of standards and support a single locus of interpretation (NIH).
- All the regulatory agencies submitted to a common examination of their enabling statutes and came to a consensus that none had clear authority to regulate.
- The committee concluded that a new law would be both required and desirable to assure that the NIH guidelines were followed in all similar research in the private sector.

A prescription for a "model" statute was thus developed. It included preemption of all other standards by federal ones and a sunset clause. This was forwarded to Secretary Califano, whose General Counsel drafted a bill. When the draft was sent through the OMB for clearance, last-minute anxiety on the part of one agency about the Secretary of HEW

having authority over the experiments conducted by its scientists, threatened to send us all back to the drawing board. The "government bill" survived to be introduced, however, but was quickly lost from sight, as I will relate later.

All the government agencies were also given liaison membership in the RAC, where the decision making under the guidelines proceeded. An Industrial Use Subcommittee was formed within the Interagency Committee, under the chairmanship of Gilbert Omenn of OSTP, to consider concerns raised by NIOSH and OSHA about the risks of industrial "scale-up" for recombinant technology.

There was considerable agency concern over "turf," rDNA being a matter of high press and public interest. Passions were controlled by augmented communication and frequent discussions. In addition to maintaining a desirable amount of ecumenical spirit within the federal bureaucracy, the Interagency Committee had the virtue of being there and ready for immediate convocation in the event one of the hypothetical hazards materialized and national resources needed to be mobilized and coordinated.

CONGRESSIONAL CAUTION

The Congress, despite the introduction of more than a dozen bills and intensive hearings on the subject, refrained from enacting a statute to control laboratory experimentation with recombinant DNA.

The activities of the Congress relative to rDNA merit a more thorough and thoughtful analysis than is possible in this paper. One would like to

explore more carefully the various motives of the legislators and their staffs that impelled them to propose legislation. Needing detailed description, too, are the hazards in drafting statutes to restrict scientific freedom in a single, highly technical area. The play of forces that ultimately led to a stalemate, no bill actually coming to a vote in either house, is a theme for several essays. There were not only conflicts over passage of new legislation, but also over interpretation of old laws to achieve the same purposes. Of particular relevance here were the attempts to make Section 361 of the Public Health Service Act (42 U.S.C. 264) the basis for nationwide regulation of recombinant DNA research. This little-used section permits the Surgeon General to take steps he deems necessary "to prevent the introduction or spread of communicable disease," a hazard of the use of rDNA technology for which there was notable absence of proof. Many members of Congress as well as the Secretary, the General Counsel of HEW, and the Surgeon General joined NIH in opposition to use of Section 361. There was a general feeling that if Congress wished to regulate laboratory experiments in biology, the members should stand up and be counted.

A rereading of the bills submitted to the 95th Congress reveals, amid the boilerplate, some intimate glimpses of tensions experienced by the sponsors. Some of the "Whereas's" were followed by dire predictions, others by acknowledgement of wondrous benefits to accompany any hazard. The kinds of fines and penalties to be assayed showed how clumsy and unrealistic are the provisions of statute for governing this kind of human activity.

The most provocative piece of legislation proposed was S. 1217 (Amended), introduced by Senator Kennedy in July 1977. The initial bill submitted in April was the Administration's minimal proposal prescribed by the Interagency Committee.

I supported the original Administration bill. It provided for federal preemption of any local regulations. This is consonant with the essential universality of science and--something more practical--it was in keeping with the absence of imminent danger to any particular community. The sunset provision of the Administration bill also was a comfort. Any legislation over so mobile an activity as scientific research should have limited life expectancy. As in the other bills, the penalty clauses were harsh and foreign to scientific research; but they were a bearable price, if we had arrived at the need for federal legislation in order to allow experimentation to proceed.

But S. 1217 (Amended) also contained a new Title XVIII establishing a National Recombinant DNA Safety Regulatory Commission. The body would be serviced by HEW but not clearly answerable to the Secretary. Of its eleven members, six were never to have engaged in molecular biology. Thus, a new administrative creation would be established to supply the consensual requirements, the majority of participants to be inexperienced in the subject matter. The Commission would set the rules (as neatly promulgated regulations), license laboratories and monitor compliance. Any extra time left over during the periodic visits of its members to Washington was consigned to a thorough analysis of "all the basic, ethical, and scientific issues involved."

The rDNA controversy excited the natural tendency to assume that dilemmas involving profound new questions should automatically be exposed to new, untested solutions. Fortunately, the maturity of our political system—or the stubbornness of its traditions, forced this complex problem to first be engaged within the existing framework of government. The DNA issue would have been gravely confounded by immediate convocation of one or another of the ad hoc commissions contained in numerous bills and articles stimulated by the controversy. One proposed that the Vice President chair the proceedings; another invoked a "science court." One thing one learns in public service is that there is not such thing as "immediate" chartering, staffing, and convening of a commission for any purpose, let alone governing the first experiments in statutory regulation of laboratory science.

One evening during the legislative furor over rDNA, I was summoned to the bedside of Congressman Olin Teague at the Naval Medical Center. "Tiger" Teague was Chairman of the House Science and Technology Committee, and he wanted a full explanation of the new biotechnology and an opinion about possible effects of pending legislation upon the progress of the science. Later, I heard how Teague had made sure that the bills to regulate rDNA by statute were jointly referred to his Committee for hearing. In so doing, he allowed tempers to cool and protected science from hasty passage of laws that would have been injurious. When NIH and HEW devised ways for industrial and other private-sector laboratories to comply voluntarily with the NIH guidelines, the pressure for legislation was nearly gone, and has never been revived.

IMAGINATIVE STRUCTURES

Government was not devoid of imagination in creating new administrative structures to permit the public a role in the DNA controversy. The "second generation" RAC was perhaps the outstanding case in point. Reorganization of this committee was a concession demanded by Secretary Califano for permission to release the first major revision of the original guidelines in December 1978. The original RAC, formed in 1975, had contained only scientists, nearly all of them molecular biologists. A political scientist was then added and somewhat later an ethicist came aboard. We initially employed the NIH Director's Advisory Committee, suitably augmented with a broad selection of scientists and laymen, as a second tier of review. It was the traditional organization selected by the Congress for the greatly expanded public support of basic research that commenced in the early 1950s.^{7/} Such a system is based on initial "peer review" (study section) followed by oversight of a group including laymen (Advisory Council) and has proved admirable for determining the allocation of resources for research. It is not effective for supervision of technical guidelines requiring continuous and rapid evolution. DNA technology was exceedingly complex material, heavy going for laymen, but also for scientists from other disciplines. Procurement of advice and approvals in two stages created confusion and added intolerable delays. Hence, the RAC was changed to collapse review into one group. Its membership was composed of one-third molecular biologists, one-third scientists who were experts on genetics, microbiology and other fields directly applicable to recombinant work, and one-third experienced in related matters such as public health, law, consumer affairs or public policy. I have observed, particularly in the technical consensus

exercises we established at NIH in the same period,^{8/} that when the non-expert is not able to comprehend much of the detail his public policy role may better be performed in the midst of the experts. Here, at least the layman can observe the experts to see if they appear to be listening to each other and paying some attention to the evidence.

The new RAC, like the first one, remained advisory to the NIH Director, who had the responsibility and authority for revision of the guidelines. Still, some of the scientists were alarmed at the new RAC as it was put into position.^{9/} Their fears of a shift of governance from the scientific to a political sphere did not materialize. I believe the new RAC was one of the most useful cultural innovations--for combining expert and non-expert opinions about science--to emerge from the rDNA controversy. Its success has been due to careful selection of members, to their generally enlightened individual performances, and above all, to the guidance of the chairmen. These have been Jane Setlow, a molecular biologist, and Ray Thornton, a lawyer and university president and once the Congressman who conducted the Science and Technology Committee hearings on recombinant DNA fostered by "Tiger" Teague.

INTERNATIONAL AFFAIRS

We were careful that NIH should not confuse its predominant place in the world of biological research with a mandate to determine the regulations that would govern rDNA research in the rest of the world. The sovereignty of each nation over its scientists was not a debatable issue. The U.S. role was both a delicate and influential one. Initially we considered it likely that there would be less controversy in most other

nations and that conditions outside the United States might well favor migration of our scientists to areas more congenial to the experimentation. It was certainly true that the extremes of reaction were observed in America and that in some countries there was little or no concern. Nearly all of the countries with advanced science and technology did adopt rules, however. The United States, Canada, and the United Kingdom were the first to have explicit guidelines. The major counterpart to the RAC proved to be the British Genetic Manipulation Advisory Group (GMAG), which set out to construct rules for the U.K. following the Ashby report. The NIH guidelines were the first of numerous different national rules to be released. Care was taken to distribute them abroad. More than 40 countries were sent the guidelines by diplomatic pouch on the day of release in 1976, accompanied by a "mission alert" from the office of Secretary of State Kissinger.

There was continuous followup. Among my papers are special travel diaries entitled "The Recombinant Odyssey." They summarize numerous visits to scientists and officials of countries which included, among others, Britain, Germany, Canada, Holland, Switzerland, the People's Republic of China, Japan, France, Sweden, Finland, Italy, and the U.S.S.R., as well as the European Economic Community in Brussels, to explain what NIH was doing and to learn how the other nations were attempting to regulate the research. I recall paying an early visit to Munich to see the new chief executive of the European Science Foundation (ESF). The late Franz Schneider informed me that he was sure the ESF would adopt the U.K. rules. Going across the city to Lynen's Max Planck Institute I found a scientist busy translating the NIH guidelines into German.

After my first visit to the British Medical Research Council and to GMAG, I realized that we were likely to achieve a kind of parity with the United Kingdom on containment rules despite a completely different mode for achieving them. The British proceeded to develop common law, case by case. The U.S. specified detailed rules in a veritable Napoleonic Code. The British met in closed rooms, protected by the Official Secrets Act. The U.S. opened the doors to everyone and compiled a massive record of the proceedings.

We worked hard to assure maximum conditions for communications and consensuality among all the users of the "new biology." Officials of the European Medical Research Council, the European community, the European Molecular Biology Organization and of the Committee on Genetics of the International Council of Scientific Unions, were often present at the sessions of the RAC and the Director's Advisory Committee, which were always open meetings. One of two major meetings which the NIH sponsored in 1977 to help clarify scientific knowledge on which the guidelines were based was held in Ascot, England so that British and continental scientists could more easily attend. The private sector, including early industrial users of the technology, and public interest groups much concerned about the activities of the former, were also tied into the loop of communications.

In fact, the NIH Office of Recombinant DNA Activities, headed by William Gartland, became the primary communicative center in the world concerning rDNA during the late 1970s. We also persuaded the Office of

Management and Budget to let us start a new journal, the Recombinant DNA Technical Bulletin, to carry the actions of RAC and scientific communications around the world. The safety manual and other advisories compiled under Emmett Barkley's direction, was another of the many technical aids devised to help standardize certain practices here and abroad. The course of GMAG in Britain and the eventual rules adopted by other countries is described by Keith Gibson elsewhere in this volume.^{10/} Most nations have adopted basically the NIH guidelines, which have remained commensurate with those of the United Kingdom.

Major differences in national standards would have precipitated a chaotic situation throughout the world--just as different regulations in the municipalities or states could have created in the United States. Indeed, had guidelines of grossly uneven character sprung up within countries or among them, the new biotechnology industry based on rDNA methods conceivably would have risen in Lichtenstein, or in the Third World, or on ships "beyond the 12 mile-limit" in the fashion of gambling casinos.

OTHER STEPS

There were many other decisions and actions for the government to take about the uses of rDNA technology. Each agency decision had to be shaped so that it could make its way past the checks and balances built into the federal process. For example, there was the decision to be made about NIH-HHS policy on patenting inventions derived from the use of genetic recombinants. Opinions were solicited and a decision made acceptable to the Secretary. Shortly I found myself before Senator Nelson, who had

strong views about patenting anything discovered through use of public funds. There was the decision to be made about how to return the authority and responsibility for using the guidelines to the institutions. The composition and function of the Institutional Biosafety Committees was another important exercise in political compromise. One of the most significant moves was the determination of how the RAC might review voluntary submissions of proprietary data from private sector laboratories interested in scale-ups. The RAC's eventual willingness to do this removed the last powerful thrust for legislation. The guidelines no longer require such examination. While they did, it was necessary regularly to persuade the RAC to continue this service, which annoyed many of the members.

It will be impossible for some of us to forget the problems engendered by compliance with the National Environmental Policy Act. The first Environmental Impact Statement on hypothetical risks of laboratory experimentation became a nightmare before it was accepted. Yet it proved invaluable in opposing the injunctions against experiments that were sought in the federal district courts. The record maintained by NIH from the inception of its role contains more history of the roles pressed upon the government and the manner in which they were played.

THE FUTURE OF THE RAC

Although we have learned that the probabilities of harmful creation from using rDNA technology are much less than some believed in 1975, no one can assign a zero probability to harmful effects now. No one should pretend we have absolutely no further need for community guidance or for

continuous evaluation of such powerful technology. It is, however, a reasonable point to ask whether the risks have not so narrowed to those already assigned to the common vectors and hosts that special containment precautions for gene engineering may now be wasteful. The problems that remain to be dealt with--such as release of recombinant organisms or plants into the environment, evaluation of the numerous products of recombinant genes, or the effecting of changes in the human genome by new techniques--are still there. But so are agencies, and other institutions to cope with the regulatory aspects of most foreseeable problems. If some of the federal regulatory forces appear to be weaker than in 1975, it would be very unwise to compensate for this by forcing NIH to assume regulatory roles it has justifiably resisted for so long.

There is a continued need for full communication and critique in the use of rDNA technology. It is the key expression of the continuity or universality of science. One would want to abandon the network of Institutional Biosafety Committees and the RAC, which lies at the center, only after ascertainment that they no longer served a useful function.

It is my view that we are not finished with practical scientific questions and ethical issues related to gene-splicing. These will not be the stuff of conventional regulation and they will require a proper place or places for the human community to debate and resolve them.

As the rules for conventional laboratory experiments inevitably slide toward the status of guidance, and as broader policy problems replace

detailed analysis of experimental protocols on the menu for its consideration, we should think about construction of a "third generation Recombinant Advisory Committee."

I suggest it might have these features:

- be designed to fill the combination tasks of the present RAC and Interagency Committees;
- be responsible to a Cabinet officer, the most appropriate still being the Secretary of Health and Human Services;
- continue to be serviced by NIH, but with broader contributions from other agencies so that the collective aspect of the future enterprise will be stressed and facilitated;
- continue to have a distinguished chairman, from the non-government sector;
- continue to have a majority of expert scientists among its members, but a total composition tailored to reflect the problems anticipated in the next few years to come.

POST-GAME CRITIQUE

I have described a number of the things that the federal government did during the rDNA controversy. Having been at or near the center of

those actions, I am not the one to judge each step or to assign a mark for the overall performance.

Such an assessment should be undertaken, however, for high science will confront big government again with similar dilemmas. We need a clear understanding of what was done and why. The design of the federal government is such that the public interest in technologies can be served without impairing the effectiveness of the scientific endeavor. This was the major civics lesson to emerge from the rDNA controversy. It was difficult, however, to maintain the proper balances, and one should not assume that the system will never fail.

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